# "A STUDY ON THE PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN GVMCH"

**A DISSERTATION SUBMITTED TO**

**THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY**

In partial fulfillment of the regulations for the award of the degree

of

**M.D. GENERAL MEDICINE – BRANCH I**

**DEPARTMENT OF GENERAL MEDICINE**

**GOVERNMENT VELLORE MEDICAL COLLEGE AND HOSPITAL**

**THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY**

**CHENNAI**

**MAY-2018**

# BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"A STUDY ON THE PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN GVMCH"** is a bonafide work done by ***Dr. SAI PRASHANTH P R ,*** Post Graduate student (2015 – 2018) in the Department of General Medicine, Government Vellore Medical College and Hospital, Vellore under the guidance of **Prof. Dr. R. THILAKAVATHI M.D.**

**Prof.Dr.R.THILAKAVATHI M.D.,**
**Guide and Chief, Medical Unit- III,**
Department of General Medicine,
Govt. Vellore Medical College

**Date:**

**Place: Vellore**

**Prof.Dr.D.ANBARASU M.D.,**
**Head of the Department,**
Department of General Medicine,
Govt. Vellore Medical College.

**Date:**

**Place: Vellore**

**Prof. Dr .M.LALITHA M.D,DA .,**
**The Dean,**
Govt. Vellore Medical College.

**Date:**

**Place: Vellore**

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| **Title of the Study** | – | A study on the Prevalence of peripheral Neuropathy in patients with Chronic Kidney disease in GVMCH. |
| **Principal Investigator** | – | Dr.P.R.Saiprashanth MD., |
| | – | Post Graduate MD (General Medicine). |

The request for an approval from the Institutional Ethical committee (IEC) was considered on the IEC meeting held on 06.10.2016 at the Conference Hall, Govt. Vellore Medical College, Vellore-11.

The members of the committee, the secretary, the Convenor and the President are pleased to approve the proposed work mentioned above submitted by the Principal Investigator.

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ETHICS COMMITTEE
Govt. Vellore Medical College
Vellore - 11.

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ETHICS COMMITTEE
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# DECLARATION

I, **DR. SAI PRASHANTH .P. R** solemnly declare that this dissertation titled **"A STUDY ON THE PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN GVMCH"** is a bonafide work done by me in the Department of General Medicine, Government Vellore Medical College and Hospital, Vellore under the guidance and supervision of Prof. **Dr.R.THILAKAVATHI M.D.**, Guide and Chief, Medical Unit-III. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the university regulations for the award of M.D., Degree (General Medicine) Branch – I.

**Place: Vellore**

**Date:** **DR. SAI PRASHANTH P.R**

# ACKNOWLEDGEMENT

It is indeed a great pleasure to thank each and every one who helped and guided me through the course of this study.

I wish to sincerely thank **Prof.Dr.M.LALITHA M.D, DA** the Dean, Govt. Vellore Medical College&Hospital for granting me permission to conduct this study and allowing me to use the available resources from this institution.

I am particularly thankful to the Chairman and members of Ethical Committee, Government Vellore Medical College and hospital for their commitment and support towards the study by granting the ethical clearance.

I express my heartfelt gratitude to my esteemed teacher **Prof Dr.D.Anbarasu M.D**, Professor and Head, Department of General Medicine for his encouragement as well as timely criticism which imparted determination and enthusiasm in me to finish this study.

I am deeply indebted to my Chief and guide **Prof Dr.R.Thilakavathi M.D**, for her active role in shaping the study without which it would not have been an easy task. With a great sense of gratitude I acknowledge the guidance rendered to me by her.

I express my sincere gratitude to **Prof Dr.S.P.Kumaresan M.D,** for his valuable input in shaping my study.

I express my deepest sense of thankfulness to my Assistant Professors **Dr.A.T.Maaran M.D**, and **Dr.G.Thirumal M.D,** for their priceless suggestions and encouragement without which the completion of this study would have been impossible.

I am very thankful to my fellow postgraduate colleagues **Dr.Netaji Sampath, Dr.Ashwini Metry** and **Dr.Thirunavukkarasu** for their friendly support in the time of need throughout the study.

It is my earnest duty to thank my **parents**, **family and well-wishers** without whom accomplishing this task would not have been possible.

Finally I would like to thank all my **patients** who were very co-operative and having had to endure and spend quite a lot of time with me for the study. They were nevertheless very enthusiastic in consenting and participating in this study in our institution.

**Place: Vellore**

**Date:** **DR. SAIPRASHANTH .P.R**

# ABSTRACT

## BACKGROUND:

The incidence and prevalence of Chronic Kidney Disease is increasing slowly. The affected groups are predominantly elderly individualS, diabetics and patients with systemic hypertension. Peripheral Neuropathy among CKD patients is the most common neurological complication of uremia, but still it is an under estimated problem adversely affecting the patient's quality of life.It is more often a silent burden for the patient, progressively affecting his/her quality of life. It is sometimes overlooked as the treating physicians are occupied with other uremia related complications and also there is a dearth of literature regarding the diagnostic criteria and management of this condition. It is further amplified by the lack of availability of a simple screening tool for peripheral neuropathy in CKD. Hence this study aims to establish the prevalence of peripheral neuropathy among patients with CKD in our Hospital.

## AIMS AND OBJECTIVES:

- To study the prevalence of peripheral neuropathy in patients with chronic kidney disease in GVMCH.
- To determine the prevalence of Peripheral Neuropathy and associated factors in relation to the stage of CKD.

## METHODOLOGY:

This study was carried out in chronic kidney disease patients attending hemodialysis unit and patients admitted as in-patients in our medical wards in the department of General medicine, Government Vellore Medical College and Hospital. A total sample of 100 patients were studied using meticulously prepared proforma over a period of one year starting from October 2016 to September 2017. After prior Institutional Ethical clearance and obtaining informed consent, the participants satisfying the inclusion criteria were asked detailed history and clinical examination was performed according to the well-designed proforma cited below. The presence of neuropathy was assessed using Michigan Neuropathy Screening Instrument (MNSI) Scores with Semmes-Weinstein monofilament(10g) and Diabetic neuropathy symptom score(DNS).Weight,height and waist of the individual patients were measured and BMI was calculated and recorded in all the cases.

## RESULTS:

The mean age of the study subjects was 47.87 years. Most of the patients belonged to the age group 40-70years.Out of 100 cases,there were 58 (58.0%) males and 42(42.0%) females.The Male to Female sex ratio was 1.38:1.Sixty patients out of 100 patients were on Hemodialysis whereas 40 patients belonged to the non-HD group. The prevalence of peripheral neuropathy in CKD patients in GVMCH assessed by MNSI was 64%.The prevalence of clinical Uremic distal symmetrical sensory-motor peripheral neuropathy assessed by MNSI in the CKD on HD population was 71.66%. Whereas the prevalence for the same for CKD patients not on HD was 73.68%.Of the non-HD patients 6 out of 17 CKD stage 4 patients(35.29% prevalence) and 1 out of 4 CKD stage 3 patients (25% prevalence)

were affected by peripheral neuropathy.The average height of the study population was 162.77cm. The average weight of the study population was 61.60kg.The average BMI of the study population was 23.05.The average eGFR of the study population was 13.05ml/min/1.73$m^2$BSA. The average serum creatinine of the study group was 5.33mgs%.

## CONCLUSION:

Uremic neuropathy is the most common neurological complication in patients with uraemia.

The condition is not restricted to patients with ESRD,but it is more prevalent in patients with stage V CKD. MNSI physical assessment could be used as a simple bed side examination to determine the presence or absence of uremic peripheral neuropathy.

**Keywords : Chronic Kidney Disease, Michigan neuropathy screening instrument, Peripheral neuropathy, Uremic neuropathy.**

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| 1. | **UPN** | Uremic peripheral neuropathy |
| 2. | **DSPN** | Distal symmetric Peripheral Neuropathy |
| 3. | **DNSS** | Diabetic neuropathy symptom score |
| 4. | **MNSI** | Michigan Neuropathy Screening Instrument |
| 5. | **CKD** | Chronic kidney disease |
| 6. | **RRT** | Renal replacement therapy |
| 7. | **SHT** | Systemic Hypertension |
| 8. | **eGFR** | Estimated glomerular filtration rate |
| 9. | **HD** | Hemodialysis |
| 10. | **NCV** | Nerve conduction velocity |
| 11. | **ESRD** | End stage renal disease |
| 12. | **BSA** | Body surface area |
| 13. | **BMI** | Body mass index |
| 14. | **PNS** | Peripheral Nervous system |
| 15. | **CRF** | Chronic renal failure |

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# INTRODUCTION

In the ever changing field of medicine, chronic kidney disease and its complications are on the uptrend in terms of incidence and prevalence and remains as a major cause of morbidity and mortality in developing and developed nations alike. It will remain to be so in the forth coming years. Much emphasis has been placed on the increased cardiovascular risk and electrolyte abnormalities that accompany chronic kidney disease but uremic neuropathy as a complication has always received less attention. The dreaded neurological complication is usually the uremic encephalopathy or a vascular event that accompanies hypertension.

The term uremic neuropathy denotes neuropathy either central or peripheral that is due to the extended effects of the spectrum of uraemia, a condition that loosely translates to accumulation of organic waste products that would be actively filtered by a normal kidney[1].

Asbury KA[1] in his own words said “The fact that chronic renal failure may be associated with polyneuropathy is not generally appreciated and is practically not documented in the medical literature. In the briefest possible terms, the neurological disease may be defined as follows: It began with painful burning sensation of the feet, followed by slowly progressive numbness and weakness. The feet and legs were affected more than the hands and arms, and the distal segments more than the proximal”. It was only after this our understanding of uremic peripheral neuropathy gradually increased.

Withstanding the therapeutic advances, most neurological complications of the uremic state fail to respond adequately to treatment.Despite routine haemodialysis, many neurological complications seldom improve in majority of the cases.

A vast spectrum of pathophysiological processes are included in chronic kidney disease (CKD), which almost always progressively lead to abnormal kidney function along with worsening glomerular filtration rate. The development of neuropathy is most common when eGFR falls below 12mL/minute/1.73m$^2$ BSA[2,3].

The estimated prevalence of CKD in India is around 0.78% -0.8%[3,4]. The rate of which is increasing slowly[1]. A rough age adjusted incidence of CKD stage V or End Stage Renal Disease (ESRD) is around 151 and 232 per million population respectively[5]. Uraemia is a clinical syndrome involving abnormalities with fluid, electrolyte, hormone balance and metabolic abnormalities. These abnormalities develop in parallel to the deterioration of renal function. Uremic peripheral neuropathy is one of the severe and disabling complications in patients with chronic kidney disease. Charcot[6] in 1880 suspected the existence of uremic neuropathy and Nearly more than half a century later, after the introduction of haemodialysis and renal transplantation in the early 1960s the investigations gathered steam. Uremic neuropathy encompasses a wide variety of manifestations of which distal symmetrical sensory motor peripheral neuropathy is the commonest. The severity of uremic peripheral neuropathy increases with decrease in glomerular filtration capacity. The neuropathy is a dying back neuropathy or central-peripheral axonopathy associated with secondary demyelination. The clinical and pathological features of uremic peripheral neuropathy were described in detail by Adams, Victor and Asbury in 1962. Dyck[7] and colleagues established the current concept of uremic neuropathy in 1971 on the basis on their wide nerve conduction studies in vivo and in vitro and on light and electron microscopy[8]. They were able to demonstrate axonal shrinkage with quantitative histology. Myelin sheaths were involved out of proportion to axonal involvement. The dysfunction of the neuron resulted in a decrease in the

diameter of the axon, rearrangement of myelin, and in the end complete degeneration of the axon. The uremic peripheral neuropathy manifestation in patients are variable ranging from paraesthesia, pain, weakness and atrophy of lower limbs, muscle cramps, restless legs to sometimes features mimicking Guillain-Barre like. Renal replacement therapy has resulted in halting of the symptoms of uremic peripheral neuropathy or even reversal but sometimes there might not be any improvement at all. The rate of reversibility depends on various parameters such as duration of symptoms, type of renal replacement therapy, frequency of dialysis and so on. Renal transplant provides the best possible results out of all the current therapies available aimed at alleviating uremic peripheral neuropathy. This study is primarily aimed at estimating the prevalence of peripheral neuropathy in patients with CKD in a tertiary care hospital including those on renal replacement therapy.

# AIMS AND OBJECTIVES

1. To study the prevalence of peripheral neuropathy in patients with chronic kidney disease in GVMCH.

2. To determine the prevalence of Peripheral Neuropathy and associated factors in relation to the stage of CKD.

# REVIEW OF LITERATURE

## INCIDENCE:

Though the occurrence of peripheral Neuropathy in patients with renal failure has been known for over a Century, it was not fully recognized till the middle of the 20th century. Before the implementation of chronic dialysis for patients with ESRD, the patients usually did not survive long enough to develop peripheral neuropathy that can be clinically diagnosed. Up to 65% of the patients develop Peripheral neuropathy, before or in a short span of time after putting them on dialysis. Nielsen studied 109 patients with CRF in Denmark, out of which 84 complained of symptoms and 56 developed signs of peripheral neuropathy[9]. Whereas, according to Bolton and Young 10% to 83% of those with CRF developed clinically appreciable neuropathy[10]. Men are more frequently affected than women. According to Nielsen, the men:women ratio was 60:49, out of 109 patients[9]. The reason behind this male preponderance is not understood yet. The occurrence of neuropathy has no association with serological and biochemical abnormalities (urea, creatinine, calcium, etc.) but has correlations with the duration and severity of renal failure[10,11]. Unlike sexual preponderance, there are no reported studies to establish the role of race.Patients of all age groups can be affected if the degree of renal failure is well established.

## ETIOLOGY OF UREMIC NEUROPATHY

The exact metabolic abnormality causing Uremic neuropathy is yet unknown.A number of observations have been made with regards to potential urotoxins that can cause peripheral neuropathy.Some of the few identified toxins are guanidine compounds, parathyroid hormone, middle molecules, myoinositol and so on.They are implicated but are not established causes of peripheral neuropathy[12].

Many had attempted to find the offending urotoxin that is precisely elevated in CKD patients causing peripheral neuropathy.In the initial days of renal replacement therapy the concept of 'middle molecules' as the likely candidate for causing uremic neuropathy was put into focus[12,13]. Though the proof was mainly observational, the concept stayed for a quite a long time[14]. The observation that dialysis considerably improves the uremic symptoms only augmented the speculation that schribner postulated that the compounds causing neuropathy should be the middle molecules with molecular weight ranging between 500 to 2000 Daltons. These compounds are however larger than Urea and Creatinine and so are cleared by dialysis at a much lower rate than urea and creatinine which are the usual measure of biochemical control of uraemia. This postulation is strengthened by the facts that the occurrence of uremic neuropathy is decreased by subjecting the patient to more number of cycles of dialysis in a week.Hemodialysis with 3 cycles a week has been able to bring about an abrupt halt in the progression of neuropathy but nevertheless the improvement was very minimal or negligible, whereas patients on peritoneal dialysis were able to experience a significant improvement in symptoms even without improvement in biochemical parameters like urea and creatinine.This could be due to the fact that the peritoneum is able to filter the middle molecules much more efficiently than the semisynthetic membranes used in hemodialysis[13]. This was reflected in a study by Raskin et al, on 30 patients out of whom 5 had peripheral neuropathy.The study could not make a convincing association between the middle molecule levels and peripheral neuropathy[11].

After 10 years, Bergstom and Furst came up with a criteria[14] for uremic toxins. Those were,

- The toxin must be identified chemically and quantitatively measured in biological fluids.
- The estimated quantity of the toxin should be higher in patients with renal insufficiency in comparison with normal individuals or patients without renal insufficiency.
- The concentration of the compound in plasma should have a positive correlation with the specific uremic symptoms and reduction in the quantity of the compounds should alleviate the uremic symptoms.
- The manifestations of the toxic compound must be evident at the levels found in plasma of patients with renal insufficiency.

Uremic neurotoxins refers to those toxic compounds that are found in plasma which has damaging properties on the function of nervous system that can be either central nervous system or peripheral nervous system[15,16].

The toxic compounds leading to uremic neuropathy can be categorized into 3 varieties they are,

- Small water soluble compounds like urea &creatinine which are not so toxic and can be easily removed by dialysis.
- Middle molecules.
- Agents that binds to proteins.

Asymmetric dimethyl arginine (ADMA), a LMW agent is implicated in pathogenesis of atherogenisis,cerebrovascular accidents and coronary artery disease[17,18,19].

Unfortunately, no single agent has been proven to have toxic effects on peripheral nerve function.Recent evidences points towards only an anatomical nerve damage possibly by combined effects of numerous uremic agents[20, 21].

Following are the compounds postulated but yet to be validated as a cause of uremic neuropathy.

**Small water-soluble compounds**

- Guanidines
- Asymmetric dimethyl arginine
- Creatinine
- Purines
- Oxalate
- Phosphorus
- Urea

**Middle, large molecules**

- Advanced glycosylated end products
- Parathyroid hormone
- Oxidation products
- Peptides (beta-endorphin, methionine-enkephalin, beta-lipotropin, granulocyte inhibiting proteins I and II, degranulation-inhibiting protein, adrenomedullin)
- Beta 2-microglobulin
- Complement factor D

**Protein-bound compounds**

- Indoles
- 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid
- Hippuric acid
- Homocysteine
- Indoxylsulfate
- P-cresol
- Polyamines

## GUANIDINE COMPOUNDS

Guanidine is one of the normal product of protein metabolism that has been termed as one of the potential uremic toxin for a long time[22]. Many different guanidine compounds are said to present in the brain of an uremic patient[23], leading to conclusions that they may have a role in the pathogenesis of Uremic encephalopathy[24]. The postulated mechanism behind guanidine related toxic activity is that it binds to N-methyl-D-aspartate receptors through guandidino-succinic acid,activation of which has been implicated in the etio-pathogenesis of various types of brain damage[25,26,27]and leading to mitochondrial dysfunction through inhibitory mechanisms[28]. In a study on cognitive impairment in hemodialysis patients by Murray et al, assessment of Guanidine compounds levels in 28 different areas of brain of uremic patients was done[29]. An interesting observation was that the Guanidinosuccinic acid level in uremic brain was 100 fold higher when compared to control brains which were normal and established a positive correlation between the brain levels of guanidinosuccinic acid and the extent of uraemia. Guanidinosuccinic acid when infused into animal brain of the amount found in uremic brain, it lead to convulsions[29].

The other effects of Guanidines include down regulation of neutrophil superoxide dismutase and decrease the response of NK cell to IL-2[30]. The Rest of the Guanidines are analogues of Arginine, and inhibits NO (Nitric oxide) Synthase competitively which can adversely hamper the removal of advanced glycation end products(AGEs)[31]. This causes constriction of blood vessels, rise in Blood Pressure, ischemic glomerular injury, impairment of immune function[32], and neurological dysfunction[33,34]. Other LMW compounds that are recently studied and are believed to be important uremic toxins are cross-linked protein products that contain Diotyrosine (AOPPs) and asymmetric dimethyl arginine (AMDA)[18, 19].

These compounds act as inflammatory mediators,hence are found to be very high chronic inflammatory states such as CKD. Asymmentricdimethyl arginine also inhibits NO and has been associated with high plasma levels of homocysteine[19].

**ADVANCED GLYCATION END PRODUCTS**

Advanced glycation end products are either proteins or lipids formed due to exposure to blood sugar. Since they fall under the toxic 'Middle Molecules category', they are not effectively removed by conventional hemodialysis and there is a progressive retention of these compounds in patients with End Stage Renal Disease[37].

Advanced glycation end products have a causative role in,

- Pathogenesis of Dialysis associated Amyloidosis[35].
- Diabetic Nephropathy[36].
- Systemic Hypertension in CKD patients by inactivating endothelial nitric oxide[38].

## PROTEIN-BOUND COMPOUNDS (TOXINS)

Polyamines like Spermine are Lipophilic protein bound compounds that are postulated to be potent uremic toxins that exerts its toxic actions through binding with NMDA(N-Methyl-D-aspartate)receptors,altering the tight ionic homeostasis leading to a terminal pathway for brain cell death [39,40,41]. These compounds accumulate in patients with renal insufficiency and are not effectively removed by haemodialysis.

## PARATHYROID HORMONE

In CKD patients there is a state of secondary hyperparathyroidism leading to increased calcium in the grey matter of the brain leading to characteristic EEG changes [42,43,44]. The hyperparathyroid state also leads to other comorbidities like coronary artery disease and associated heart failure and cerebrovascular accidents[48,49]. Surprisingly these effects were observed in canines administered with parathyroid hormone while keeping serum calcium and phosphate in normal range.The dogs with renal insufficiency too displayed similar brain calcium levels and EEG abnormalities and parathyroidectomy prevented the further progression of brain calcium and EEG abnormalities,Hence, it was postulated that the parathyroid hormone was essential in producing uremic neuropathy in canines[45, 46].

Primary hyperparathyroidism usually presents as neurologic or psychiatric illness even in the absence of renal insufficiency[50-53] and produce EEG alterations similar to what is found in Acute Renal Failure[42-54]. EEG changes appear within eighteen hours of manifestation of acute renal failure and remains unaltered by dialysis for 2 months[42]. Parathyroidectomy causes reversal of EEG and psychiatric manifestations in patients with either primary or secondary hyperparathyroidism, further consolidating the fact that the parathyroid hormone has a direct adverse action on

CNS producing neuropsychiatric manifestations. Renal replacement therapy by decreasing brain calcium levels has significant positive impact on EEG abnormilities[42-46]. The above understanding of pathogenesis of CNS derangement in hyperparathyroidism gives better picture but is not a comprehensive one. The raised calcium in tissues like skin, cornea, blood vessels, brain, and heart in those with hyperparathyroidism shows that parathyroid hormone somehow causes the influx of calcium into these tissues leading to specific manifestations.

Finally calcium is an indispensible tightly regulated ion that has a very important role in neurotransmission but any disruption in the calcium levels in the brain can affect normal neuronal transmission leading to abnormal brain function. Animal and human studies have perfectly explained the role played by hyperparathyroidism as one of the important pathogenic process of uremic encephalopathy and other CNS disturbances in patient with either ARF or CKD[55, 56].

**TRANSKETOLASE**

It is a Vitamin B1 dependent enzyme found in erythrocytes and nerve tissue that takes part in pentose phosphate pathway. The RBC transketolase function appeared to be depressed due to accumulation of LMW compounds in patients with CKD which might lead to neuropathy[11].This has been evident from the fact that there is an abrupt rise in transketolase activity in post dialysis blood compared to pre-dialysis blood.The Neuropathy in pre-dialysis patients could not be attributed only to the depressed transketolase levels alone, as it is not known whether depressed plasma levels of other vital enzymes may have had an added role, or even downregulated transketolase activity is indeed the absolute cause of peripheral neuropathy.Hence it remains as an important postulated mechanism rather than an established one[57, 58, 59].

**MYOINOSITOL**

Hypermyoinositolemia in Chronic kidney disease is also implicated in the pathogenesis of uremic neuropathy. Myoinositol is a water soluble cyclic hexitol that forms phosphoinositide. These phosphoinositides has increased metabolic activity in neural tissues affecting the functionality of nervous tissue, hence their accumulation in CKD is speculated to be an important cause of uremic neuropathy. Structurally it consists of 6 carbons arranged in a ring containing alcohol group. The molecular weight is 180 Daltons. Phosphoinositides, a phospholipid compound, can be synthesized from myoinositol. Their presence in nerve is said to affect its function. The renal system may have a main role in both myoinositol breakdown and removal.

Studies revealed direct correlation among blood urea nitrogen in blood and myoinositol levels. High myoinositol levels in blood of rats achieved by feeding a diet with 35% per-cent myoinositol caused decreased motor NCV(nerve conduction velocity) in the sciatic nerve. The motor NCV returned to normal levels following replacement with a diet low in myoinositol. In short, Hypermyoinositolemia may cause a decrease in nerve conduction velocity but its absolute role in uremic neuropathy as an uremic toxin has not yet been fully ascertained[7,10,11].

**PATHOLOGIC FEATURES:**

Uremic neuropathy is primarily an axonopathy caused due to decreased energy supply by inhibiting enzymes required to maintain energy production as postulated by Fraser and Arieff.[60]Pathological research on uremic neuropathy is far and few when compared to the clinical research. Most of these were sural nerve biopsy studies. Specific structural derangement in uremic neuropathy is not well understood although there are many researches; where demyelination is reiterated.Asbury et al[1], postulated

that neuropathy is similar to axonal degeneration of other causes. Since it is an axonopathy, the nerve fibres which are long are affected compared to shorter fibres because the metabolic needs of the peri-karyon with a longer fibre is not adequately met in comparison with the shorter fibres.This results in dying back neuropathy. The nodes of ranvier which have greater demand due to saltatory conduction and axonal transport are more affected than other parts of nerve fibres. Nielsen[9], postulated that peripheral nerve derangement was due to disruption of axonal membrane function and depression of Na+/K+ -activated ATPase by urotoxins.

Bolton[10] theorized that membrane derangement may occur in perineurium, acting as a diffusion barrier between interstitium and the neuron, or within the endoneurium, that function as a interface between blood and neuron. The end pathway is an direct nerve damage by urotoxins in the endoneurium causing water and electrolyte shift leading to either expansion or retraction of space.

A study by Dyck et al[7]concluded that the uremic neuropathy is an axonopathy affecting all sizes of nerve fibres but the larger and most distal nerve fibres are predominantly affected.Although it is believed that segmental demyelination do take place,rapid nerve regeneration obscures the demyelinating phase. Electron microscopic changes reveals splitting of the myelin lamellae, and detachment of lamella from subjacent axolemma with smaller mitochondrial abnormalities. Neurofilamental or neurotubular derangements are not usually seen. These changes are found in any number of neuropathy and are not exclusive to Uremic neuropathy[8].

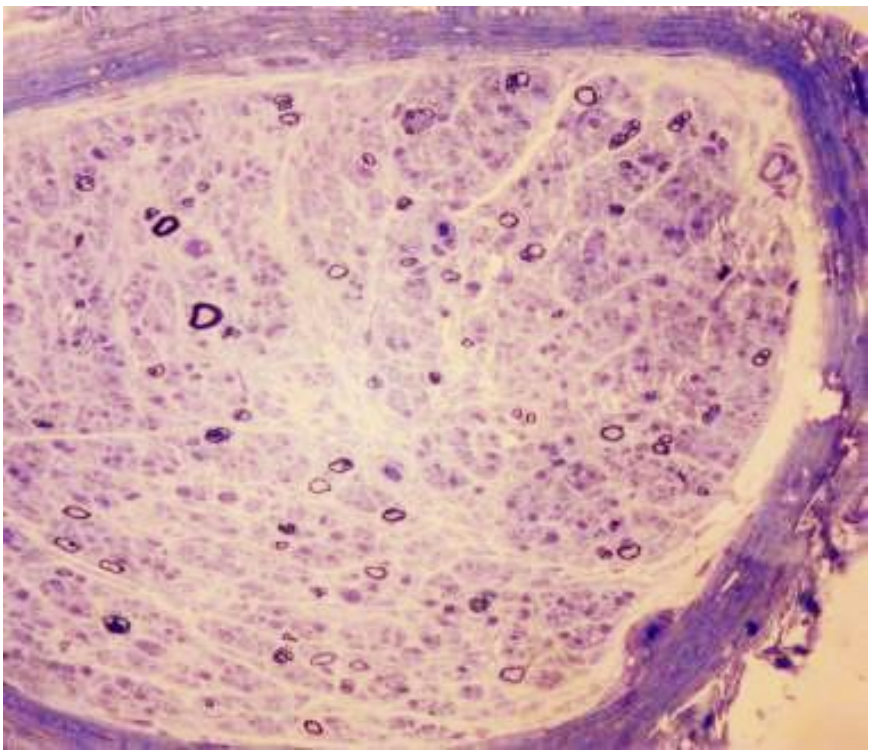


Figure.1 Semithin cut section of Sural nerve with uremic neuropathy having extreme axonal destruction of big and tiny neurons. The biopsied nerve is stained with Toluidine blue, 200X magnification.

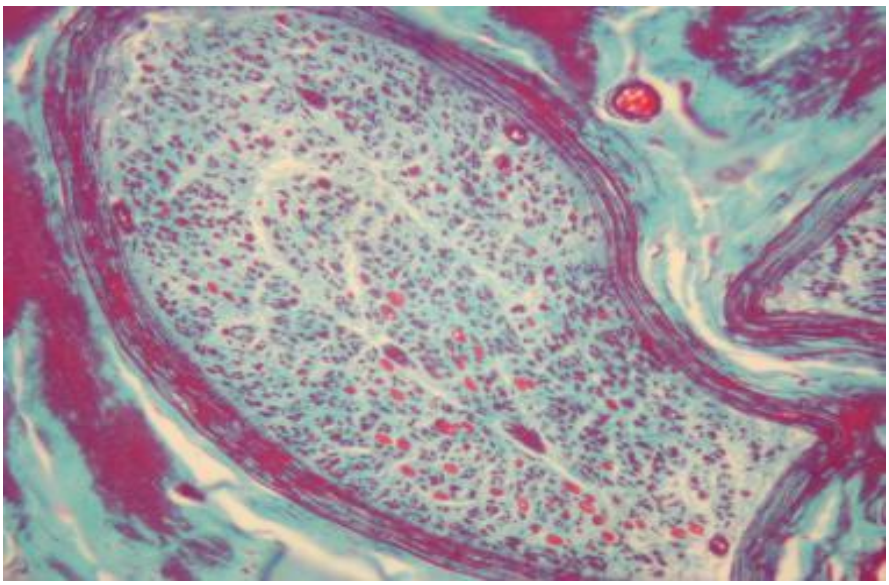


Figure 2: Modified Gomori Trichrome-stained sural nerve in uremic neuropathy. The same nerve showing severe demyelination. 200X magnification.

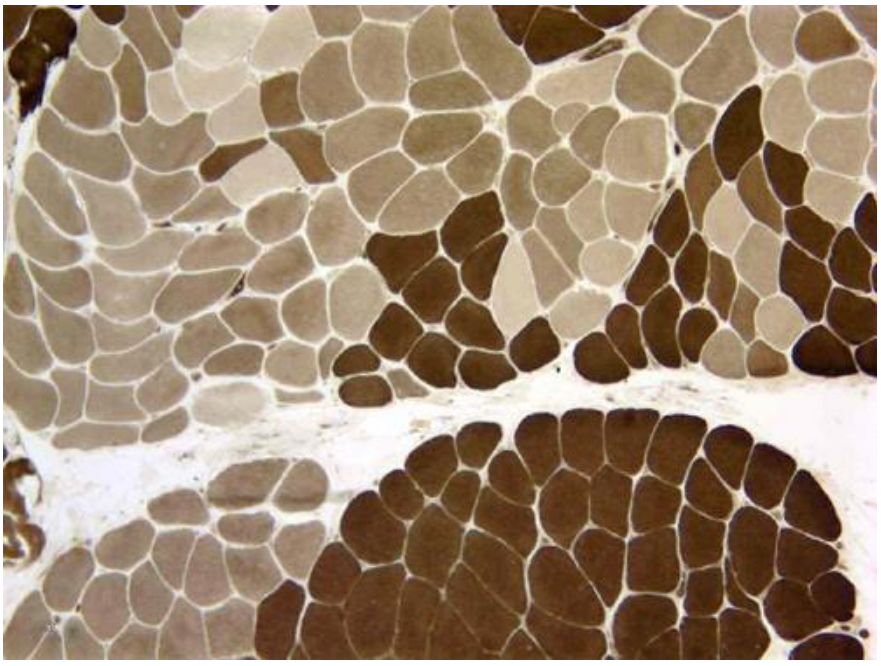


Figure 3: Muscle biopsy in uremic neuropathy with ATPase stain (pH 9.4). The normal muscle mosaic pattern was replaced by fiber type grouping, which suggested chronic denervation and reinnervation. 100X magnification.

## CLINICAL FEATURES

Uremic neuropathy has a vast spectrum of neurological manifestations but the most common manisfestation of uremic neuropathy is distal symmentrical, mixed motor and sensory polyneuropathy.Since it is predominantly an axonopathy the longer axons are affected first manifesting as predominantly involving lower limb more than the upper limb.The degree of peripheral neuropathy depends on a lot of factors including the duration of renal insufficiency, eGFR, duration of dialysis and so on. These variables have little effect on the predominant presentation of uremic neuropathy[8].The restless leg syndrome is characterized by crawling and prickling sensations in lower limbs particularly more in the evening and are relieved by only changing the lower limb position.The restless leg syndrome is one of the first symptoms signifying the involvement of peripheral nerves in uremic neuropathys.[11,60] Nielsen[61] in his study had seen the above features in 41 out 109 patients with various stages of CKD. Callaghan as quoted by Asbury and Thomas[62] consider them to be an important early sign of peripheral nerve damage. Whereas some others are reserved in claiming the restless leg syndrome as a significant symptom since some studies showed that even an equal amount of patients without peripheral neuropathy can have restless leg syndrome. Muscle cramps of the extremities is an important symptom in patient with chronic kidney disease.Muscle cramps can also occur in patients with acute kidney injury more frequently on patients on haemodialysis.This probably reflects the fluid shift between the muscle and vascular compartment and the effect of uremic toxins at the neuromuscular junction[11].'Burning feet' similar to those occuring in alcoholics are as per Tytler[63], an usual initial sign of neuropathy, but Neilson[61] showed that only 6% of 109 victims have those complains, whereas 44 of his patients experience other sensory features.

Many patients with uremic neuropathy have poorly defined dysesthesias of distal extremities most frequently uncomfortable raw sensations or rarely tingling and electric shock like sensations precipitated due to subtle digital stimulation,

The other even rarer vague sensations that uremic patients frequently complain are band like constrictive feelings compressing the feet and ankles or abnormal feeling of distension and turbulence of the fingers or toes or the peripheries that are spiralled into awkward positions[8].

The classical signs that are commonly present in patients with peripheral neuropathy are impaired vibration sense in lower limbs,impaired joint position sense and loss of deep tendon reflexes[8,11,61].The progression of peripheral neuropathy shows wide variations among patients.With early peaking of symptoms and sings and gradual progression along with decrease in eGFR or remaining stationary even with worsening renal failure [8].

Spencer and Schaumberg termed it as 'dying-back polyneuropathy[64]. The etiology of these central-peripheral axonopathies are due to different varieties of toxins. The axonopathies comprises of neuropathies related to diabetes, multiple myeloma, amyloidosis, some hereditary polyneuropathies and uremia.[64] Spinal cord especially the posterior column and few more areas of CNS are also involved along with peripheral nervous system manifestations. The clinical manifestations of distal axonopathies in CNS as postulated by Schaumberg and Spencer[64,65] are:

- Peripheral neuropathy of insidious onset due to continuous exposure to low concentration of toxin in plasma leading to slowly progressive distal axonopathy but a normal functioning limb.

- Large and long axons of the nerves of the lower limbs are affected more in compared with the upper limb.Sciatic nerve fibres are affected more in comparison with the others.
- Classical glove and stocking distribution of sensory loss is usually seen affecting the feet and hands initially.
- Absence of Achilles tendon reflex occurs earlier in comparison with others.This is due to the fact that axonal fibres to calf muscles are comparatively larger to the smaller axons to the feet.
- Nerve conduction velocity is significantly affected in demyelinating lesions,whereas it is normal or slightly affected in case of axonopathy which can have scattered intact motor fibres.
- CSF findings are within the normal range and since the pathologic alterations are mostly in distal nerves the nerve roots remain unaffected.
- Uremic neuropathy has a very slow recovery time after the initiation of dialysis which is characteristic of axonal neuropathies.Axonal neuropathies have a prolonged recovery time in comparison to demyelinating neuropathies.
- In conjunction with the peripheral large fiber changes there may be associated changes in the large fibres like pyramidal tracts and spinocerebellar tracts of central nervous system.The manifestations of central tracts remain less apparent due to concomitant peripheral neuropathy, however during the recovery phase of peripheral neuropathy the signs are unmasked and there may be spasticity or ataxia respectively.
- Many toxic axonopathies have destruction of neurons in the CNS with associated destruction in the peripheral nervous system. Clinical features of damage in the corticospinal and spinocerebellar pathways could not be

clinically evident if there is extreme peripheral neuropathy. However, on healing from the neuropathy, there could be spasticity or ataxia.

Spencer and et al [66,67] have demonstrated that most toxic compounds which are chemically unrelated can cause similar patterns of distal symmetric polyneuropathy in both humans and animals.From the wide research that was conducted researchers believe that there is a common end pathway by which toxins cause axonopathy .

Failure to meet the metabolic demands of the distal axon due to decreased enzyme activity in the presence of toxins followed by decreased delivery of necessary enzymes to distal axon causing a decreased concentration of enzymes in distal region.This could all lead to a local blockade of energy dependent axonal transport, which is the harbinger of a pathway that finally ends in distal nerve fiber degeneration. Patients with CKD with uraemia who also have associated comorbidities like Diabetes mellitus, oxidative stress, with accumulation of superoxides and AGEs(advanced glycation end products) have greater propensity to have uremic neuropathy[9,17].Desert hedgehog mRNA was found to be decreased in experimental studies involving diabetic neuropathy,which dramatically improved on treatment with sonic hedgehog igG fusion protein. Such a mode of therapy can be tried successfully in uremic neuropathy[68].

Uremic myopathy is also an important cause of fatigability in CKD patients frequently causing myopathic weakness and exercise limitation.It is characterized by muscular atrophy in the final stages[69, 70].

Peripheral neuropathy is divided into two broad classes.The first category is a distal symmetrical mixed sensory-motor polyneuropathy which has a glove and stocking type of distribution of sensory loss and motor weakness that is more distally in the extremities.These type of neuropathies are of the dying back variety of axonopathy

which affects the axons that are the largest and the longest hence involving distal parts of legs and hands.These distal symmetrical sensory motor mixed polyneuropathies have toxic compounds, paraneoplastic and metabolic derangements as their etiological agents.The other type may be a mononeuropathy or multiple mononeuropathies which causes a focal isolated lesion of peripheral nerves. The distal symmetrical polyneuropathy(DSPN) is one of the most common forms of uremic peripheral neuropathy but uremic neuropathy is not exempt from a wide array of neuropathic presentations other than DSPN.

Peripheral neuropathy only occurs as an end result to a common pathogenic pathway and hence is not as a whole unique to a distinct set of disorders like diabetes,chronic alcoholism,vitamin deficiency states and so on. Uremic polyneuropathy is only a result of renal insufficiency and accumulation of toxic metabolites,it has no relationship with the type of renal syndrome that affects the kidney function.Certain conditions has a simultaneous effect on peripheral nerves as well as other target organs, these include SLE, amyloidosis, PAN (Polyarteritisnodosa), diabetes mellitus, hepatic failure and multiple myeloma.The general consensus is that the clinical manifestation of uremic neuropathy is usually silent if the glomerular filtration rate is above 12ml/min/1.73$^2$BSA.

Most CKD patients with uremic neuropathy who are asymptomatic often show positive signs for neuropathy on physical examinations.Neuropathies may also manifest in the form of autonomic dysfunction in the form of impotency,orthostatic hypotension.Many patients exhibit subclinical neuropathy with decrease in nerve conduction velocities in the absence of neuropathic symptoms and signs. Electrophysiological evidence of peripheral neuropathy does not always dictate anatomical change in nerves .The autonomic dysregulationis often a neglected part of

uremic neuropathy which may explain the blood pressure fluctuations in patients with chronic renal insuffeciency[71].

To summarize,

- Uremic peripheral neuropathy is an insidious onset slowly progressive distal neuropathy predominantly presenting with complaints of tingling, prickling, pins and needles sensations and restless leg syndrome.
    - Paraesthesia is one of the common and initial clinical presentations.
    - Hyperalgesia is an important symptom.
    - Paresis and atrophy of the muscles of lower extremities closely follow the sensory symptoms .The dying back axons in due time involve proximal group of muscles and starts to involve the upper limb
    - Muscle cramps and restless legs syndrome which is characterized by bizzare crawling sensations ,quickly resolving with change in limb posture were reported to involve 67% of patients with uremic neuropathy patients,although it is also found in patients without uremic neuropathy.
- In extremely rare cases a GBS like presentation has been reported with rapid progression to respiratory failure.The limb weakness develops over days to week with hyporeflexia.
    - Compressive mononeuropathies in the form of carpel tunnel syndrome, cubital tunnel syndrome or peroneal nerve compression at fibular head can also occur.
    - Peripheral nerves which are partly involved are more often the affected ones in compressive mono neuropathies

- In amyloidosis deposition of amyloid material can be found in carpel tunnel aiding in median nerve compression leading to carpel tunnel syndrome.
- AV fistulas may compromise blood flow to nerves leading to distal ischaemic mono neuropathies

**EFFECT OF DIALYSIS ON PERIPHERAL NEUROPATHY**

The course of peripheral neuropathy in patients with CKD depends mainly upon eGFR before dialysis[11, 72,73,74,75].Peripheral neuropathy if severe before the initiation of renal replacement therapy has less chance of improvement after hemodialysis or only improves partially.If the peripheral neuropathy is mild there is a chance of complete recovery with subsequent cycles of haemodialysis.In patients with ESRD neuropathy progression remains stationary or improves only slightly.Peritoneal dialysis due to its advantage in removing middle molecules more effectively seems to impart a better prognosis in patients with CKD.

**INTERMITTENT PERITONEAL DIALYSIS:**

Intermittent PD is a time and resource consuming modality of renal replacement therapy.The usual duration and frequency is 12-24 hour of PD delivered by a cycler in a hospital or in-center setting, 2-3 times per week.IPD might be a favourable option for elderly patients who are not fit for Haemodialysis or PD at home due to associated co-morbidities.The advantages of IPDs are fewer episodes of peritonitis and better prognosis[76]. A trial of IPD is often advised in patients for whom palliative therapy alone might seem inadequate[77].

**HEMODIALYSIS:**

Patients with CKD on HD have various different manifestations of peripheral neuropathy with an estimated prevalence of (60%-75%).The most common symptom of peripheral neuropathy in patients with CKD is paraesthesia found in nearly 6% to 32% of patients. Hemodialysis may halt the progression of uremic neuropathy or may even cause rapid reversal of neuropathy[78-82].

**RENAL TRANSPLANTATION**

Renal transplantation offers the best possible cure for uremic neuropathy,as evident from studies which showed to normal clinical and electrophysiological features following successful renal transplantation.The normal functioning nephrons quickly detoxifies the plasma leading to initial rapid remission followed by a slow phase. In a study by Nielson et al conducted on 22 patients with uremic neuropathy who underwent renal transplantation, There was a rapid recovery in clinical symptoms and signs and electrophysiological features.The recovery is better in the distal segments than in the proximal segments. Bolton et al[83] emphasized the superiority of Renal transplantation over hemodialysis in the management of Uremic polyneuropathy. Whereas, in some cases the injury is permanent and cannot be reversed even on long term dialysis.[84]

**ELECTRODIAGNOSIS**

Electrophysiological study is the Gold standard method in assessing peripheral nerve function[7].Preswick in 1964 [85] has demonstrated that decrease in conduction velocity is a common finding in uremic cases with no external manifestations of neuropathy. Jebsen[86], demonstrated inverse relation between serum creatinine and nerve conduction velocities.

Many viable urotoxins have been discovered which has decreased the motor nerve conduction velocity (MNCV) in experimental animals. [87, 88] The MNCV has been a principle test for determining neuron function, inspite of fact that it has its own defects. The associated pitfalls in using MNCVs to diagnose peripheral neuropathy are

1) Cyclical variations[89] in MNCVs that can alternatively show normal values on one day and abnormal values on another day.

2) These day to day variations can reach as high as 20%.

3) The plasma uremic toxins found in animals which caused a decrease in MNCVs was not reproducible in humans.[90-93]Nielson et al,concluded that a decrease in eGFR and a decrease in motor nerve conduction velocities have a positive correlation with appearance of clinical neuropathy[20,94]. In patients not on HD, serum creatinine had a positive correlation with reduction in nerve conduction velocities.The demonstrated slowing was typically generalized, motor and sensory, proximal and distal and in both upper and lower limbs. Several researchers have postulated that before the apparent decrease in motor nerve conduction velocities there was abnormal late responses utilizing the tibial and peroneal H-reflex and F-wave studies.Hence these H-wave and F-wave studies are the best and early indicators of electrophysiological deterioration in patients with chronic kidney disease on long term hemodialysis[95,96,97].

# MATERIALS AND METHODS

**DESIGN:**

Cross sectional study

**STUDY POPULATION:**

This study was carried out in chronic kidney disease patients attending hemodialysis unit in our hospital and patients admitted as in-patients in our medical wards in the department of General medicine, Government Vellore Medical College and Hospital.

**SAMPLE SIZE:** 100 Chronic Kidney Disease patients

**STUDY PERIOD:** OCTOBER 2016 to SEPTEMBER 2017

**INCLUSION CRITERIA**:

- All patients irrespective of age and sex with the chronic kidney disease.
- eGFR<60ml/min/$1.73^2$ determined by

  MDRD formula (186.3 x (Creatitine in mg/dl)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female)
- Ultrasound abdomen evidence of CKD(increased renal cortical echogenicity, reduced renal cortical thickness or reduced renal length <9cm)

All patients included in the study had chronic kidney disease. Defined as abnormalities of kidney structure or function for 3 months or longer with implications for health (KDIGO 2012 CKD NOMENCLATURE). The patients were further classified based on glomerular filtration rate (GFR) criteria of 30-59ml/min/1.73m2 (Stage III),15-29 ml/min/1.73m2(Stage IV) and GFR <15ml/min/1.73m2 (Stage V or End Stage Renal Disease).Patients at the time of

evaluation were on medical management or on Hemodialysis 4hr duration & 3 cycles per week. None of the patients were on peritoneal dialysis.

**EXCLUSION CRITERIA:**

- Patient denying Consent
- Patients who had a renal transplant
- Patient with other known cause of peripheral neuropathy such as Hypothyroidism, Alcoholism, Diabetes Mellitus, Tuberculosis, Hansen's disease, Patients on drugs having peripheral neuropathy as established toxicity, malignancy and vitamin B12 deficiency.

**METHODOLOGY:**

Patients after satisfying the inclusion criteria were included in the study and were asked detailed history regarding the duration of uremic symptoms, whether the patient is already on any renal replacement therapy, if the patient is already on hemodialysis then the duration of his hemodialysis period was recorded. The patients were asked to answer questions from MNSI questionnaire and DNSS questionnaire. Then physical assessment according to MNSI physical assessment chart was carried out and points filled.

**ETHICAL CLEARENCE:**

This study was approved by the ethical committee of Government Vellore Medical College and Hospital, Vellore-11.

**STATISTICAL ANALYSIS:**

Statistical analysis was done using the SPSS v16 software. The prevalence is expressed in percentage (%). Quantitative data were expressed in mean, minimum, maximum and standard deviation. The qualitative data was expressed by Chi-Square test. The difference was considered statistically significant if p value was $\leq 0.05$.

**OPERATIONAL GUIDELINES**:

Peripheral neuropathy was considered to be present if

1. ≥7 points in MNSI QUESTIONNAIRE
2. ≥3 points in MNSI PHYSICAL ASSESSMENT SCORE
3. ≥1 points in DNS SCORE

Dyslipidemia was considered to be present if:

1. Total cholesterol ≥ 200 mg/dl

2. Triglycerides ≥ 150 mg/dl

## RESULTS AND ANALYSIS

During the period of study, 100 patients diagnosed to have chronic kidney disease were included in the study after satisfying the inclusion criteria and the following observations were made.

## AGE:

The mean age of the study group was 47.87±14.76 years, with a minimum of 16 years and a maximum of 84 years. Most of the patients belonged to the age group of 40-70 years of age.

**SEX:**

Out of 100 cases, there were 58(58.0%) males and 42(42.0%) females. The Male to Female sex ratio was 1.38:1.

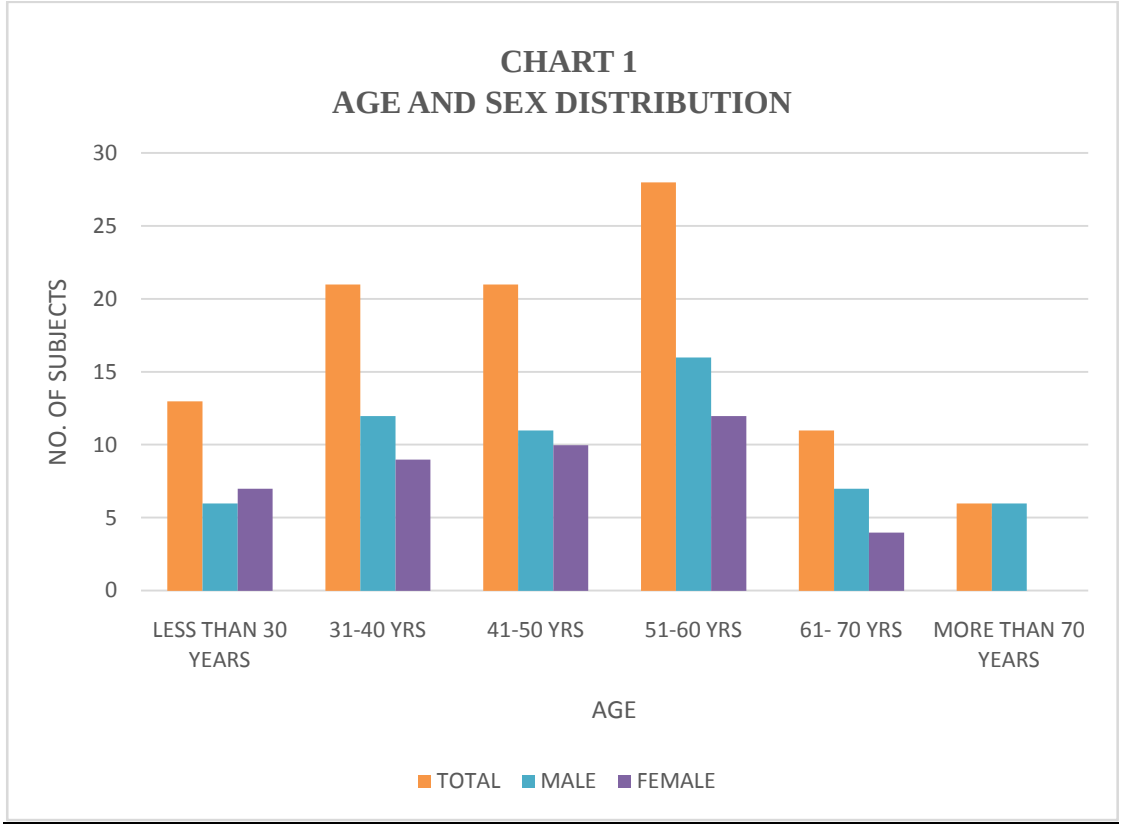
**AGE AND SEX DISTRIBUTION:**

Of the total number of patients, there were 7 patients who belonged to the age group of 15-25years, of which there were 4 males and 3 females.A total of 17 patients belonged to the age group of 26-35 years of age of which there were 8 males and 9 females.There were 16 patients who belonged to the age group of 36-45 years of age of which there were 9 males and 7 females.27 patients belonged to the age group of 46-55 years of age of which 15 patients were male and 12 patients were female.

A total of 24 patients belonged to the age group of 56 to 65 years of age of which 15 were males and 9 were females.7 patients belonged to the age group of 66 to 75 years of age of which 5 were males and 2 were females and finally 2 patients belonged to 76 to 85 age group of which both were males.

## TABLE 1:AGE and SEX DISTRIBUTION

| AGE (IN YRS) | MALE | FEMALE | TOTAL | PERCENTAGE(%) |
|---|---|---|---|---|
| <30 | 6 | 7 | 13 | 13.0% |
| 31-40 | 12 | 9 | 21 | 21.0% |
| 41-50 | 11 | 10 | 21 | 21.0% |
| 51-60 | 16 | 12 | 28 | 28.0% |
| 61-70 | 7 | 4 | 11 | 11.0% |
| >70 | 6 | - | 6 | 6.0% |

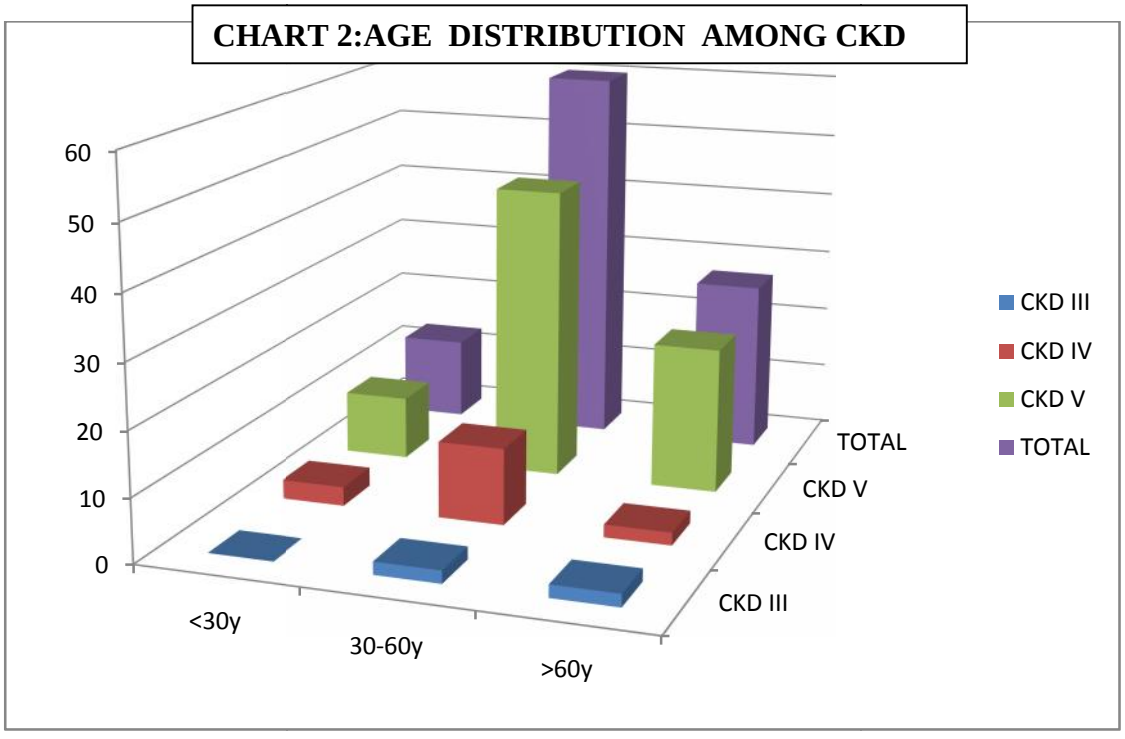


## AGE and SEX DISTRIBUTION AMONG DIFFERENT CKD SUBCLASS:

### TABLE 2: AGE DISTRIBUTION IN CKD SUBCLASSES

| AGE in years | CKD STAGES | | | TOTAL |
|---|---|---|---|---|
| | III | IV | V | |
| <30y | 0 | 3 | 10 | 13 |
| 30-60y | 2 | 12 | 46 | 60 |
| >60y | 2 | 2 | 23 | 27 |
| TOTAL | 4 | 17 | 79 | 100 |

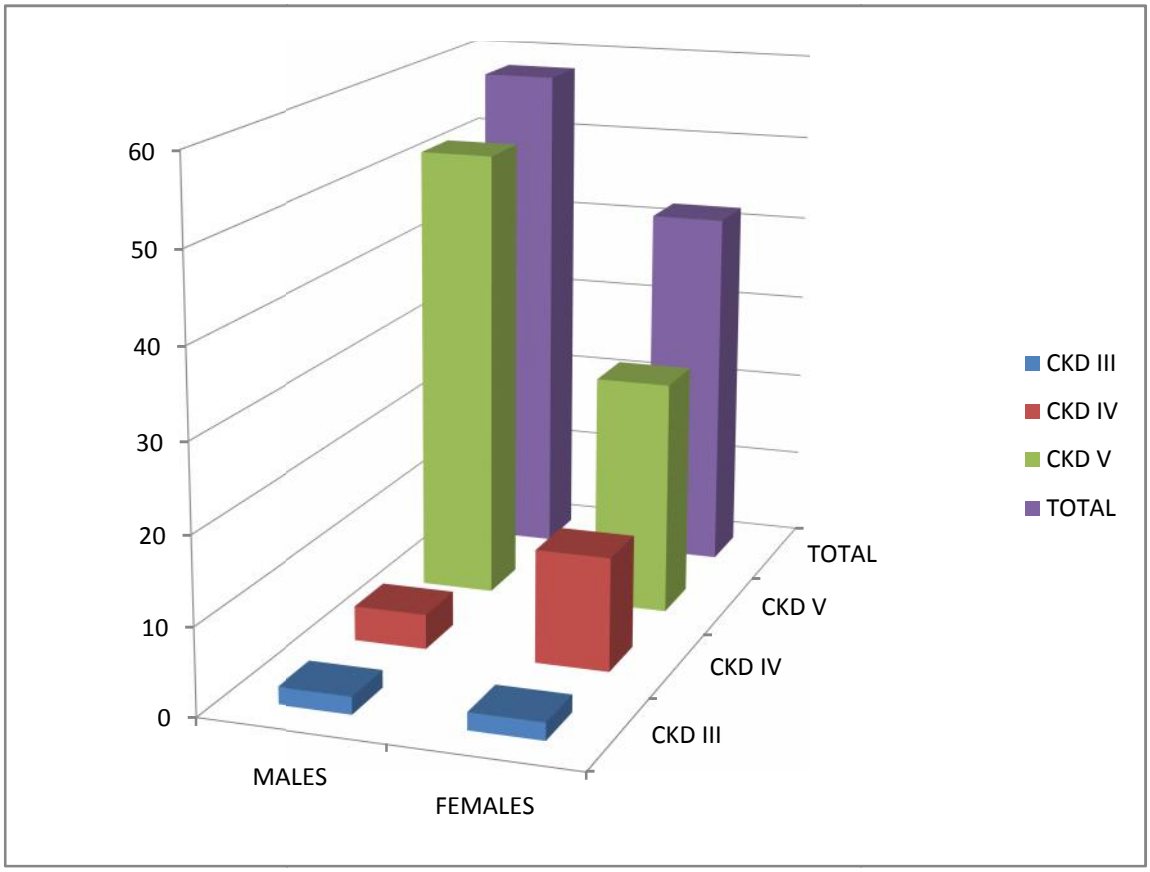
**CHART 2:AGE DISTRIBUTION AMONG CKD**



## TABLE:3GENDER DISTRIBUTION IN CKD SUBCLASSES

| GENDER | CKD STAGES | | | TOTAL |
|---|---|---|---|---|
| | III | IV | V | |
| MALES | 2 | 4 | 52 | 58 |
| FEMALES | 2 | 13 | 27 | 42 |
| TOTAL | 4 | 17 | 79 | 100 |

## CHART:3 GENDER DISTRIBUTION CHART IN CKD SUBCLASSES



# PREVALENCE OF UREMIC PERIPHERAL NEUROPATHY

## DISTRIBUTION OF UPN IN THE STUDY POPULATION:

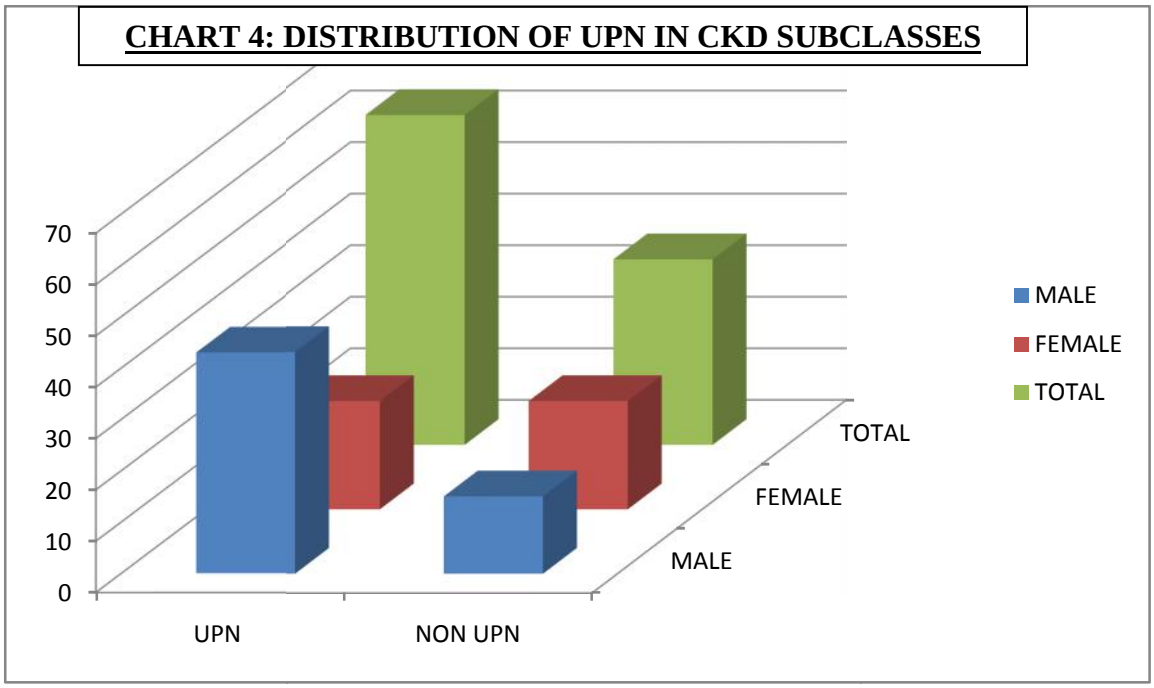
In the study population out of 100 patients, 64 patients were found to have clinical uremic peripheral neuropathy.The distribution of uremic neuropathy in different sub groups of study population is as follows.

Out of 100 patients 4 (4.0%)patients belonged to STAGE III CKD out of which 1 patient (25% prevalence) patient was clinically found to have peripheral neuropathy.17(17.0%) patients belonged to stage IV CKD group out of which 6 patients (35.29% prevalence) clinically tested positive for peripheral neuropathy.The CKD stage V group which includes both patients on HD and patients not on HD treatment had the highest number of patients at 79(79.0%) out of which 57 patients (72.15% prevalence) clinically tested positive for peripheral neuropathy.

**TABLE:4 DISTRIBUTION OF UPN IN CKD SUBCLASSES**

| | Clinical UPN -ve | Clinical UPN +ve | Total |
|---|---|---|---|
| CKD stage III | 3 | 1 | 4 |
| CKD stage IV | 11 | 6 | 17 |
| CKD stage V | 22 | 57 | 79 |
| TOTAL | 36 | 64 | 100 |

**CHART 4: DISTRIBUTION OF UPN IN CKD SUBCLASSES**




**AGE DISTRIBUTION:**

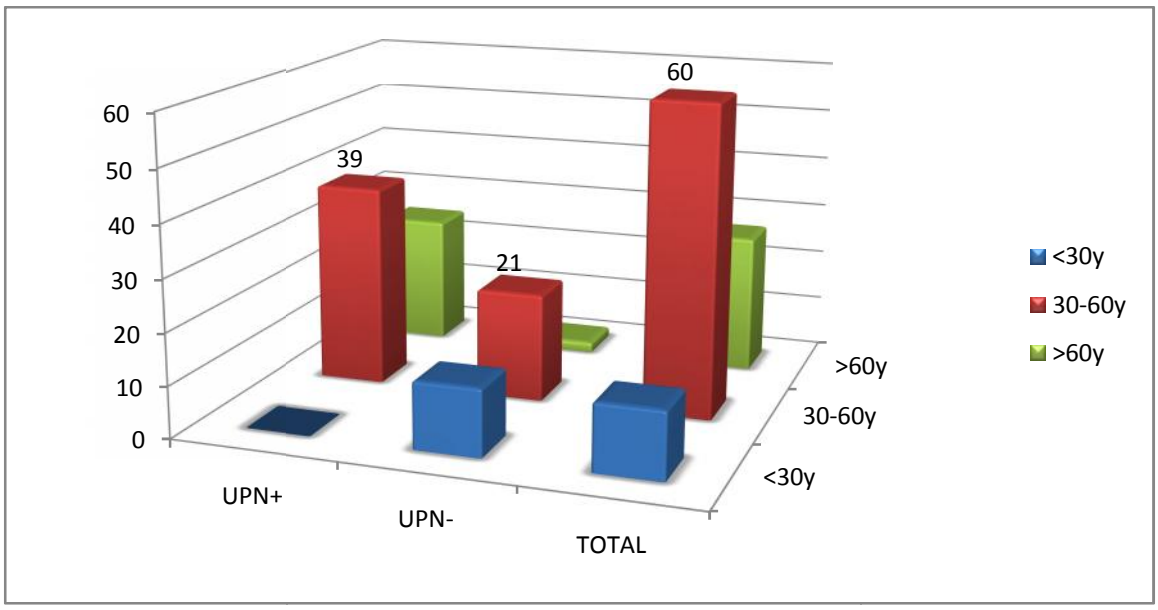
Among the 13 patients who belonged to the age group of <30 years, none of the patients were affected by peripheral neuropathy.3 patients among them belonged to CKD stage 4 group and 10 patients among them belonged to CKD stage 5 group.

**TABLE 5: AGE & UPN DISRIBUTION**

| AGE | UPN | | TOTAL |
|---|---|---|---|
| | **PRESENT** | **ABSENT** | |
| **<30years** | 0 | 13 | 13 |
| **30-60years** | 39(65%) | 21 | 60 |
| **>60years** | 25(92.5%) | 2 | 27 |
| **Total** | 64 | 36 | 100 |

Among the 60 patients who belonged to 30-60years age group 39 patients (65%) were affected by peripheral neuropathy among them 2 patients belonged CKD stage 3 group,12 patients had stage IV CKD and 46 patients belonged to CKD STAGE V group.The prevalence of UPN was increased among older patients particularly among the patients aged more than 60 years.This was statistically significant $\chi^2$=32.718 with 2 degree of freedom and the p value was< 0.01.

**CHART 5: AGE & UPN DISTRIBUTION CHART**



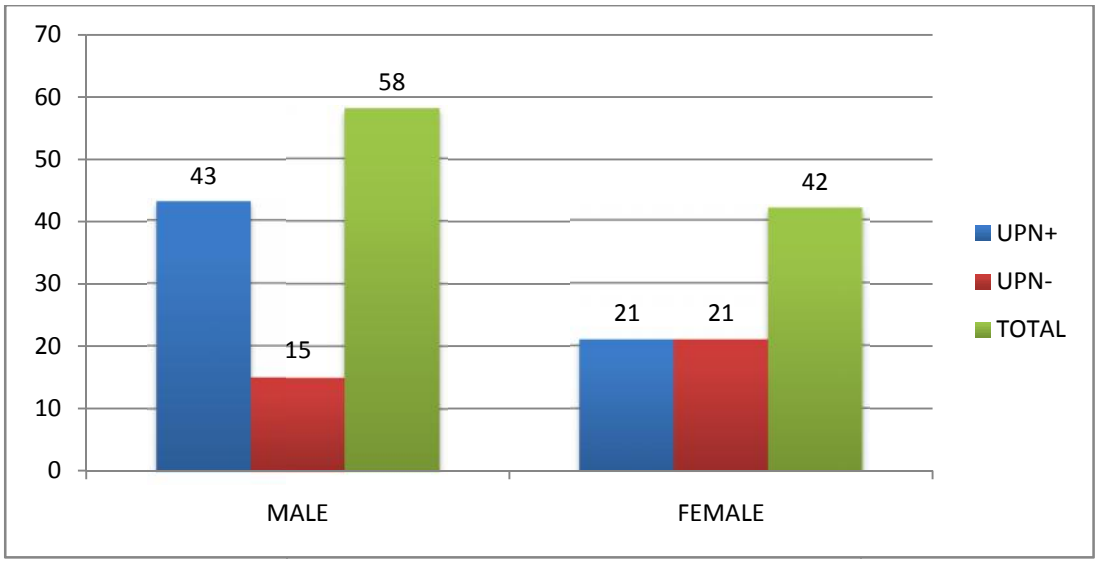

**GENDER DISTRIBUTION OF UPN:**

In the study population among 58 male patients,43 males(74.13) were affected and among 42 females,21 patients(50%) were affected by uremic neuropathy. The males were affected more when compared to females and this was statistically significant. $\chi^2$=6.160 with 1 degree of freedom and p value=0.013(<0.05)

**TABLE 6: GENDER AND UPN DISTRIBUTION**

| GENDER | UPN | | TOTAL |
|---|---|---|---|
| | **PRESENT** | **ABSENT** | |
| **MALE** | 43 | 15 | 58 |
| **FEMALE** | 21 | 21 | 42 |
| **Total** | 64 | 36 | 100 |

**CHART 6:GENDER DISTRIBUTION**




**CKD STAGE V group:**

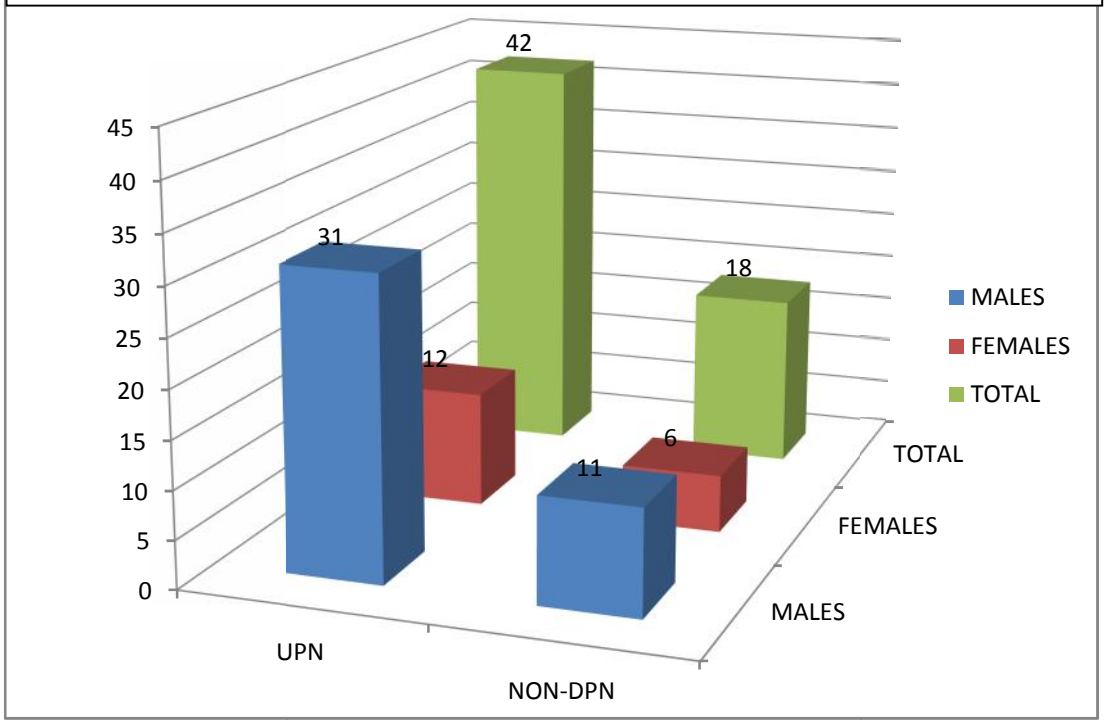
There were a total of 79 patients who belonged to stage V ckd group, out of which 60 patients were on Hemodialysis and 19 patients were not on Hemodialysis during the time of study.

In the HD group out of 60 patients,43 patients(71.6%) were diagnosed as having clinical peripheral neuropathy and 17 patients(28.33%) had not satisfied the diagnosis of clinical peripheral neuropathy.Within respective sexes 31 males(73.80%) and 12 females(66.66%) had peripheral neuropathy. Out of the 43 patients, 31 patients who had peripheral neuropathy were males(72.09%) and 12 patients were females(27.90%) ,whereas, out of 17 patients who did not have peripheral neuropathy 11 were males(26.20%) and 6 were females(33.33%).

**TABLE 7: CKD V (on HD) & UPN**

| CKD V(on HD) | **UPN** | | **TOTAL** |
|---|---|---|---|
| | **PRESENT** | **ABSENT** | |
| **MALE** | 31(73.80%) | 11(26.20%) | 42 |
| **FEMALE** | 12(66.66%) | 6(33.33%) | 18 |
| **TOTAL** | 43 | 17 | 60 |

**CHART 7: UPN DISTRIBUTION CHART IN CKD STAGE V(ONHD)**



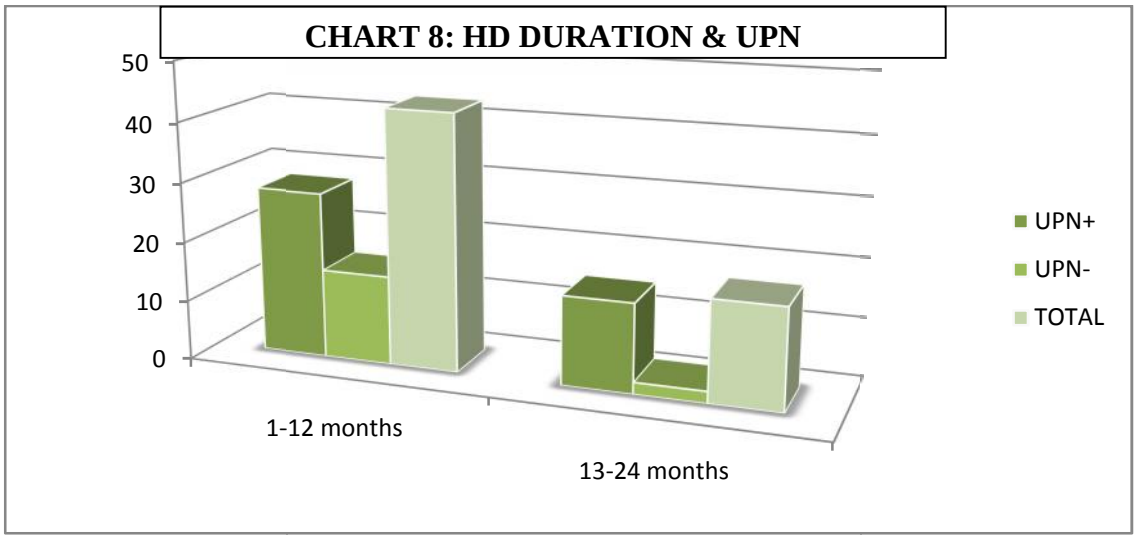

The Chi square value was $\chi^2$=3.827 and the p value was exactly 0.05, hence statistically significant in the study population.

**Duration of HD and UPN**:

The Minimum duration of HD was 2 months and the maximum duration was 24 months with a mean of 6.50 months±6.829. Out of 43 patients who had a HD duration between 1-12 months the peripheral neuropathy was present in 28 patients and in patients having HD duration between 12 to 24 months the peripheral neuropathy was present in 15 patients

## TABLE 8: UPN & HD DURATION

| HD DURATION | UPN | | TOTAL |
|---|---|---|---|
| | PRESENT | ABSENT | |
| **1-12 months** | 28(65.11%) | 15 | 43 |
| **13-24 months** | 15(88.23%) | 2 | 17 |
| **TOTAL** | 43 | 17 | 60 |




There presence of peripheral neuropathy and Duration of HD was not statistically significant. $\chi^2$=0.41 with 1 degree of freedom and p value=0.840(p value >0.05).

**CKD STAGE V (Not on HD group)**

Out of 79 STAGE V CKD patients,19 patients(24.05%) were not on Hemodialysis.

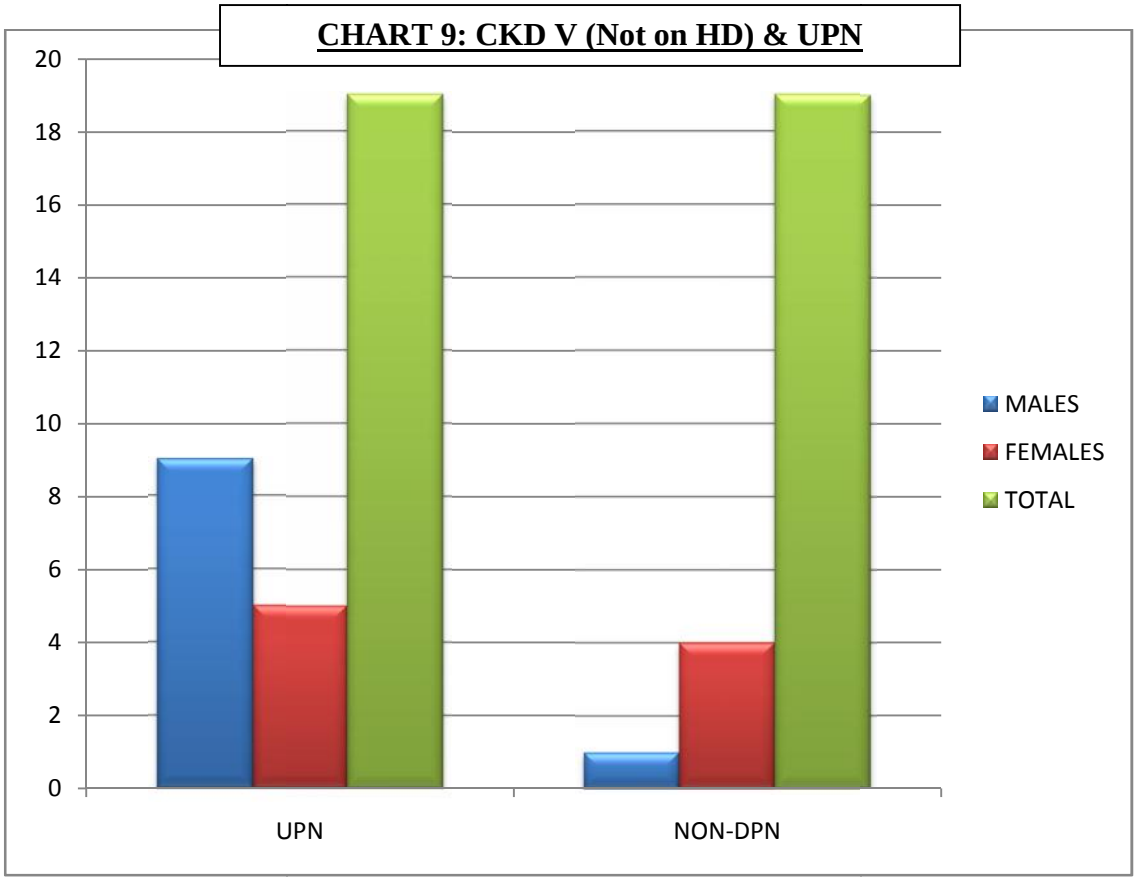
Among them were 10 males(52.63%) and 9 females(47.36%).

A total of 14 patients(73.68%) out of 19 patients had evidence of peripheral neuropathy and 5 patients(26.31%) did not have peripheral neuropathy.

## TABLE 9: CKD V (Not on HD) & UPN

| | UPN | | TOTAL |
|---|---|---|---|
| | PRESENT | ABSENT | |
| **MALE** | 9(90%) | 1(10%) | 10 |
| **FEMALE** | 5(55.55%) | 4(44.44%) | 9 |
| **TOTAL** | 14 | 5 | 19 |

## CHART 9: CKD V (Not on HD) & UPN



Within respective sex, 9 males(90%) had peripheral neuropathy and 5 females(55.55% ) had peripheral neuropathy.Among 14 patients who tested positive for peripheral neuropathy 64% were males and 35.71% were females.

Prevalence of uremic neuropathy in CKD V not on HD was statistically significant. $\chi^2$=10.999 with 2 degrees of freedom and p value=0.004(<0.01)

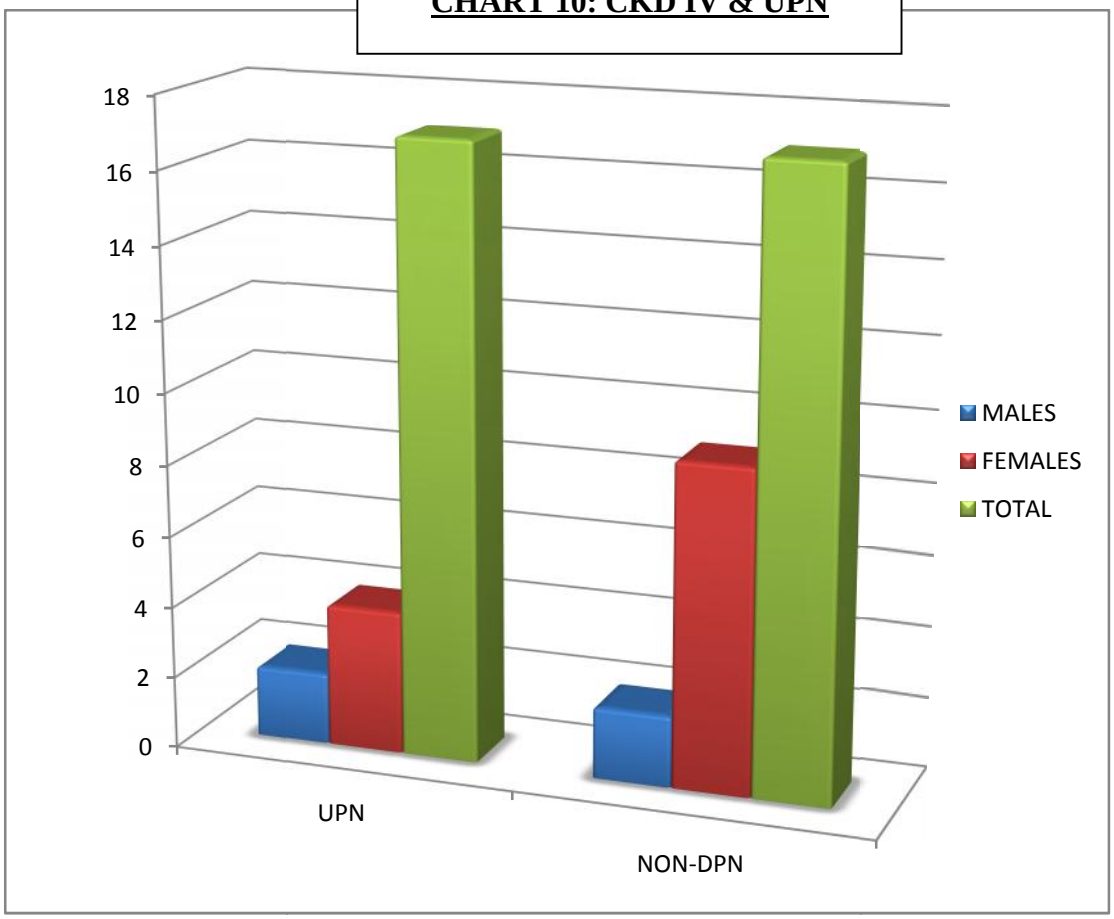
**PERIPHERAL NEUROPATHY IN STAGE IV CKD:**

There were a total of 17 cases who belonged to CKD stage IV, of which there were 4 male and 13 females.Out of the 17 patients 6 patients were diagnosed with peripheral neuropathy.The prevalence of peripheral neuropathy was 35.29%(p value <0.01).Among males the prevalence was 50% and among females the prevalence was 30.76% which was statistically significant $\chi^2$=10.999 ,p value=0.004(<0.01)

**TABLE 10:CKD IV & UPN**

| CKD STAGE IV | UPN +ve | UPN -ve | TOTAL |
|---|---|---|---|
| MALES | 2(50%) | 2(50%) | 4 |
| FEMALES | 4(30.76%) | 9(69.23%) | 13 |
| TOTAL | 6(35.29%) | 11(64.70%) | 17 |

**CHART 10: CKD IV & UPN**



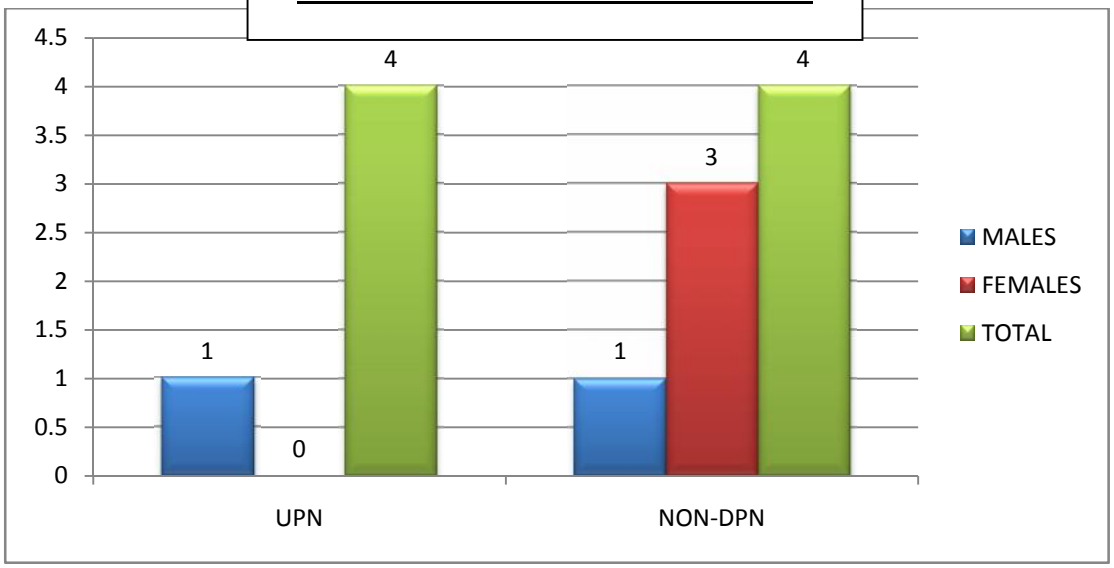

**PERIPHERAL NEUROPATHY IN STAGE III CKD:**

There were a total of 4 cases who belonged to stage III CKD,among them were 2 males and 2 females.Out of these 4 patients,1 male patient had peripheral neuropathy.None of the female patient had evidence of clinical peripheral neuropathy.Hence the prevalence of peripheral neuropathy in STAGE III CKD patient was 25%.In the study sample 1 of the male patient was affected and none of the females were affected. The prevalence of peripheral neuropathy in CKD III was statistically significant. $\chi^2$=10.999 with 2 degrees of freedom and a p value=0.004(<0.01).

**TABLE 11: CKD III & UPN**

| CKD STAGE III | UPN +ve | UPN -ve | TOTAL |
|---|---|---|---|
| MALES | 1 | 1 | 2 |
| FEMALES | 0 | 2 | 2 |
| TOTAL | 1(25%) | 3(75%) | 4 |

**CHART 11: CKD STAGE III & UPN**



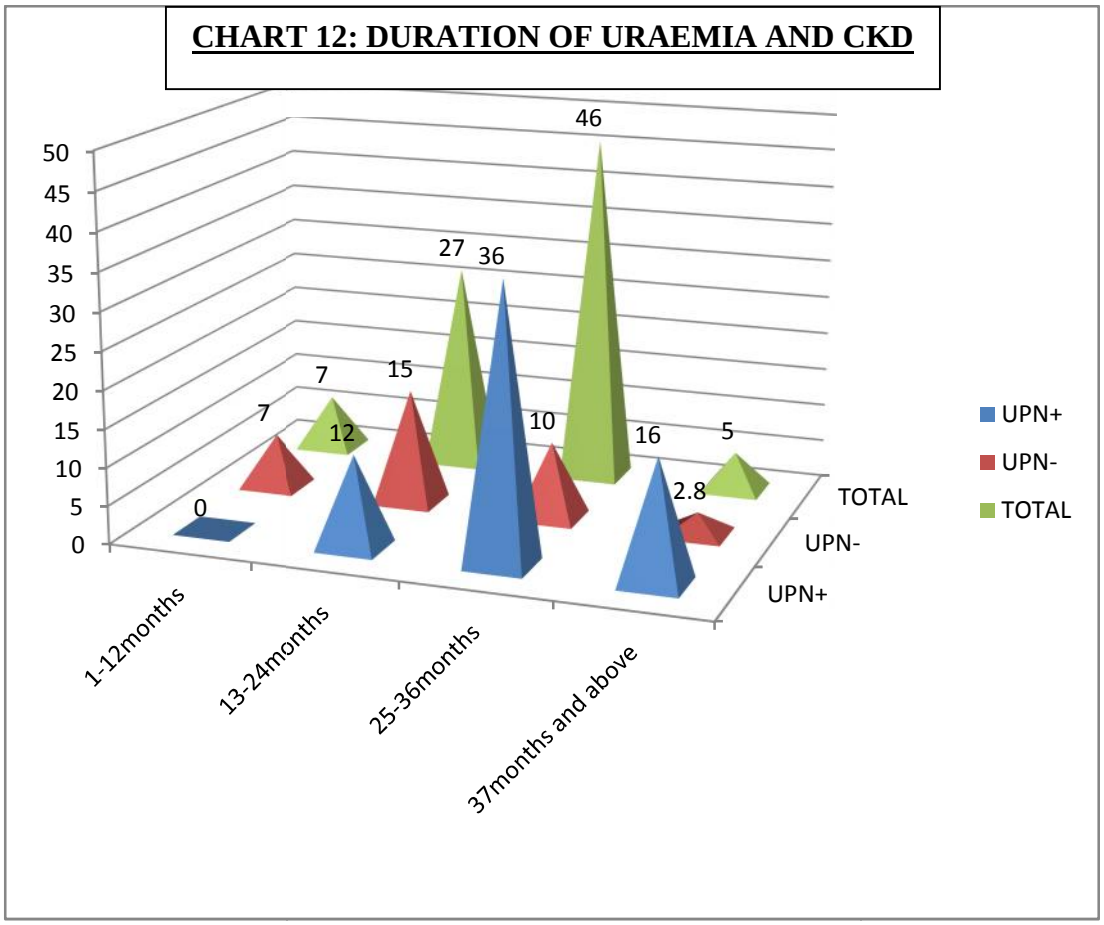

**DURATION OF URAEMIA AND UPN**:

The mean duration of uraemic symptoms and peripheral neuropathy was 28.69 months ±10.561 with a minimum of 6 months duration with a maximum of 52 months duration.

## TABLE 12: DURATION OF URAEMIC SYMPTOMS DISTRIBUTION

| DURATION OF URAEMIA (in months) | UPN | | TOTAL |
|---|---|---|---|
| | YES | NO | |
| 1-6 | 0 | 1 | 1 |
| 7-12 | 0 | 6 | 6 |
| 13-18 | 4 | 9 | 13 |
| 19-24 | 8 | 6 | 14 |
| 25-30 | 15 | 7 | 22 |
| 31-36 | 21 | 3 | 24 |
| 37-42 | 6 | 3 | 9 |
| 43-48 | 8 | 1 | 9 |
| >48 | 2 | 0 | 2 |

**CHART 12: DURATION OF URAEMIA AND CKD**




The prevalence of uremic neuropathy was 0% in patients with uremic symptom duration less than a year. It was 44% in patients with symptom duration ranging from 13 to 24 months,78.26% in patients with duration of 25 to 36 months and 80% in patients with symptoms more than 3 years.The prevalence of uremic peripheral neuropathy was more in patients with longer duration of uremic symptoms.This was statistically significant $\chi^2$=28.453 with a p value=<0.01

**EGFR AND UPN:**

The mean eGFR of the patient was 13.05 ml/min/1.73$^2$ BSA ±5.93.the maximum and minimum values are 38.39 ml/min/1.73$^2$ body surface area and 4.76ml/min /1.73$^2$ body surface area respectively.

**TABLE 13:DISTRIBUTION EGFR**

| eGFR(ml/min/1.73m$^2$BSA) by MDRD | UPN | | TOTAL |
|---|---|---|---|
| | +ve | -ve | |
| <15 | 57 | 22 | 79 |
| 15-30 | 6 | 11 | 17 |
| 30-60 | 1 | 3 | 4 |
| Total | 64 | 36 | 100 |

The prevalence of UPN was 72.15% on patients with eGFR less than 15 ml/min/1.73m$^2$BSA, It was 35.29% in patients with eGFR between 15-30ml/min/1.73m$^2$BSA

And 25% in patients with eGFR between 30-60 ml/min/1.73m$^2$BSA

The prevalence of peripheral neuropathy increased with decrease in eGFR values. this was significant statistically. $\chi^2$=10.999 with 2 degree of freedom with p value 0.004(<0.01)

**SERUM CREATININE AND UPN:**

The minimum creatinine value observed was 1.7mg/dl, the maximum creatinine value observed was 11.3mg/dl. The mean creatinine value was 5.33mg/dl±2.088

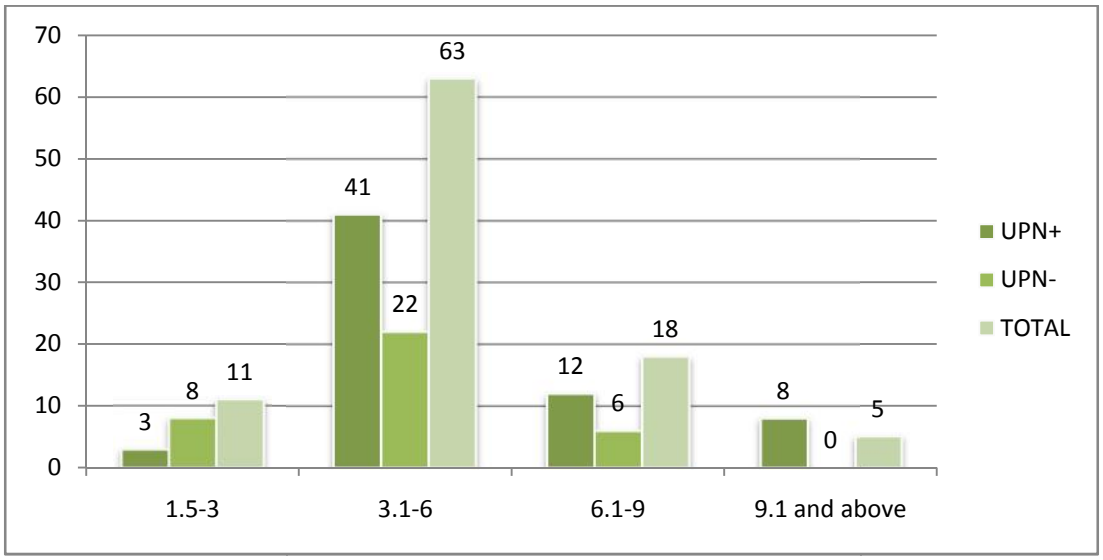
## TABLE 14:SERUM CREATININE DISTRIBUTION

| Serum creatinine In mg/dl | UPN | | TOTAL |
|---|---|---|---|
| | +ve | -ve | |
| 1.5-3 | 3 | 8 | 11 |
| 3.1-6 | 41 | 22 | 63 |
| 6.1-9 | 12 | 6 | 18 |
| 9.1 and above | 8 | 0 | 8 |
| Total | 64 | 36 | 100 |

In the study group 3 patients who had serum creatinine levels between 1.5-3mgs%, 3 patients had peripheral neuropathy (27.27% prevalence).In patients who had serum creatinine between 3.1 to 6.0 mgs%, 41 patients(65.07% prevalence) had uraemic neuropathy and in patients who had serum creatinine between 6.1 and 9mgs%, 12 patients had uraemic neuropathy(66.66% prevalence).

Finally in patients with serum creatinine above 9.1mgs% the prevalence of uraemic neuropathy was 100%.This was statistically significant $\chi^2=11.027$ with 3 degree of freedom with p value=0.012(<0.05)

**CHART 13: PERIPHERAL NEUROPATHY AND SERUM CREATININE DISTRIBUTION**




**MNSI AND URAEMIC PERIPHERAL NEUROPATHY**:

The smallest MNSI score obtained in the study population was 0 and the largest score was 7 with a mean score of 2.580 with a standard deviation of 2.069.

In the study population, 2 patients (2%) have scored MNSI scores between 1-2.5 out of 10 and 58 patients(58%) had scored between 3-5.5 out of 10.

No of Patients who had scored between 6-10 points were 34 patients. Rest of the patients have not scored any points in MNSI

**TABLE 15: THE MOST FREQUENT SIGNS OBSERVED**

| S.No | Abnormal MNSI signs | Percentage |
|---|---|---|
| 1 | Appearance of Feet | 0% |
| 2 | Ulcerations | 4.12% |
| 3 | Absent ankle relex | 40.20% |
| 4 | Absent Vibration perception | 21.64% |
| 5 | Abnormal Monofilament test | 34.02% |

Absent ankle reflex was the most common finding in the study. The second most common finding in the study was Abnormal monofilament test which was followed by absent vibration perception.

**Age distribution of MNSI scores:**

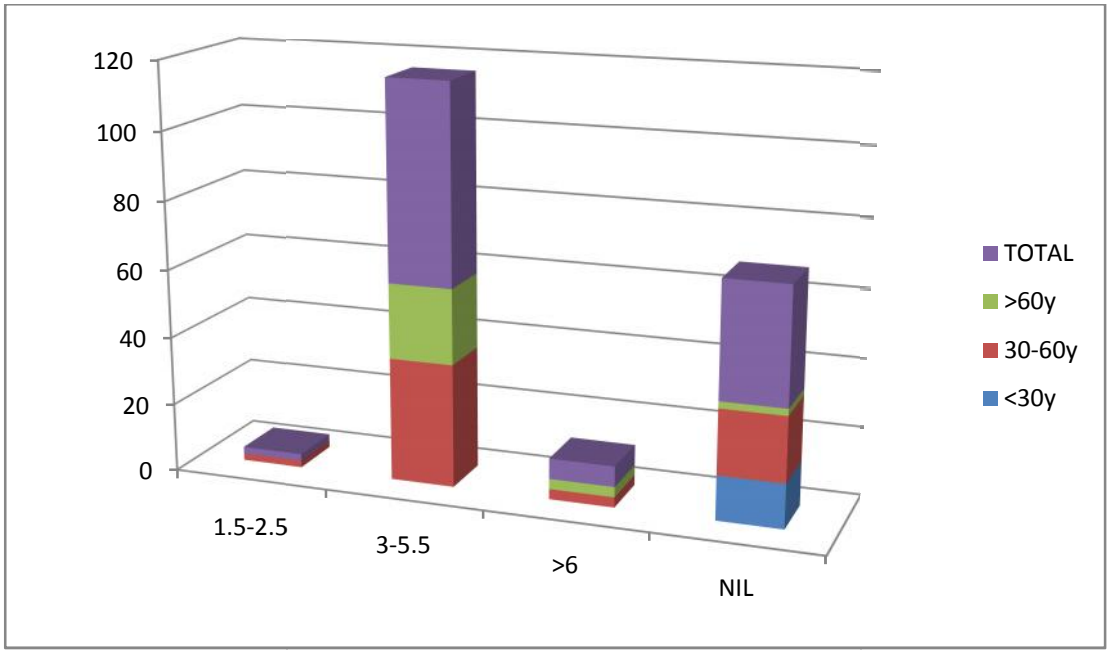
In the age group of 30-60, 2 patients (3.33%) had scored between 1.25-2.5,

36 patients (60%) had scored between 3-5.5 and 3 patients (5%) had scored greater than 6.The rest of the patients did not score any points.This was statistically significant $\chi^2$=35.904 with 6 degree of freedom p value:0.000(<0.01)

**TABLE 16: AGE AND MNSI SCORE**

| MNSI SCORES | AGE in years | | | TOTAL |
|---|---|---|---|---|
| | <30 | 30-60 | >60 | |
| 1.5-2.5 | 0 | 2 | 0 | 2 |
| 3-5.5 | 0 | 36 | 22 | 58 |
| 6-10 | 0 | 3 | 3 | 6 |
| 0 | 13 | 19 | 2 | 34 |
| TOTAL | 13 | 60 | 27 | 100 |

**CHART 14: AGE DISTRIBUTION OF MNSI**

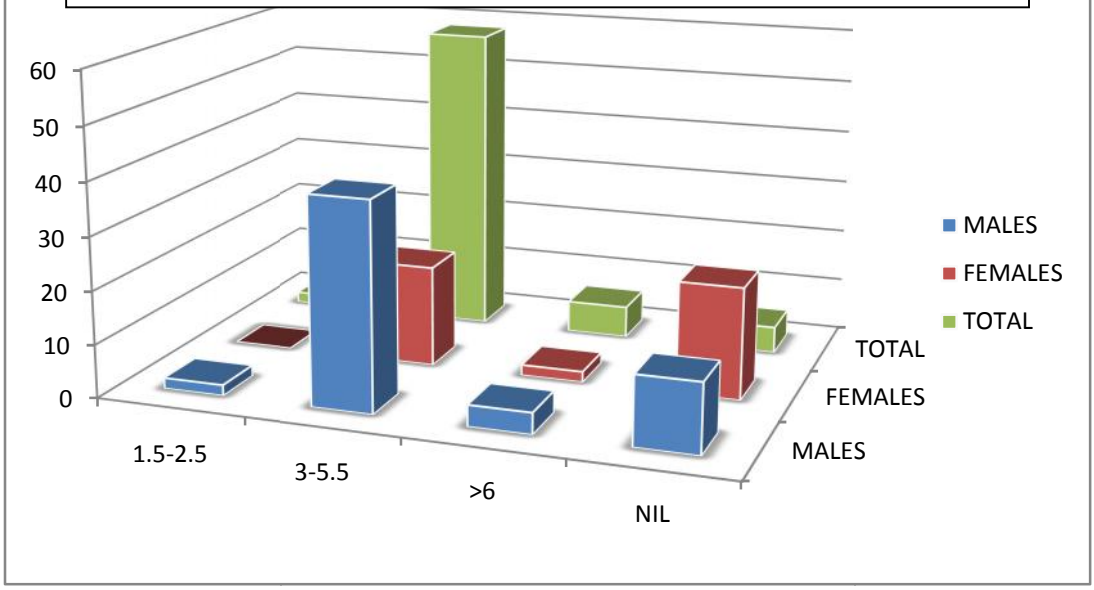


## TABLE 17: GENDER DISTRIBUTION OF MNSI

| MNSI SCORES | GENDER | | TOTAL |
|---|---|---|---|
| | MALE | FEMALE | |
| 1.5-2.5 | 2 | 0 | 2 |
| 3-5.5 | 39 | 19 | 58 |
| 6-10 | 4 | 2 | 6 |
| NIL | 13 | 21 | 34 |

Among 100 patients, 2 males have scored between 1.5-2.5, Thirty nine males have scored between 3-5.5.Four males have scored between 6-10 and 13 males have not scored any points. Among females none had scored between 1.5-2.5,Nineteen patients had scored between 3-5.5.Two patients had scored between 6-10.The prevalence of MNSI scores among genders were statistically significant $\chi^2$=9.119 with 3 degree of freedom and p value =0.028(<0.05)

**CHART 15:GENDER DISTRIBUTION OF MNSI SCORES**



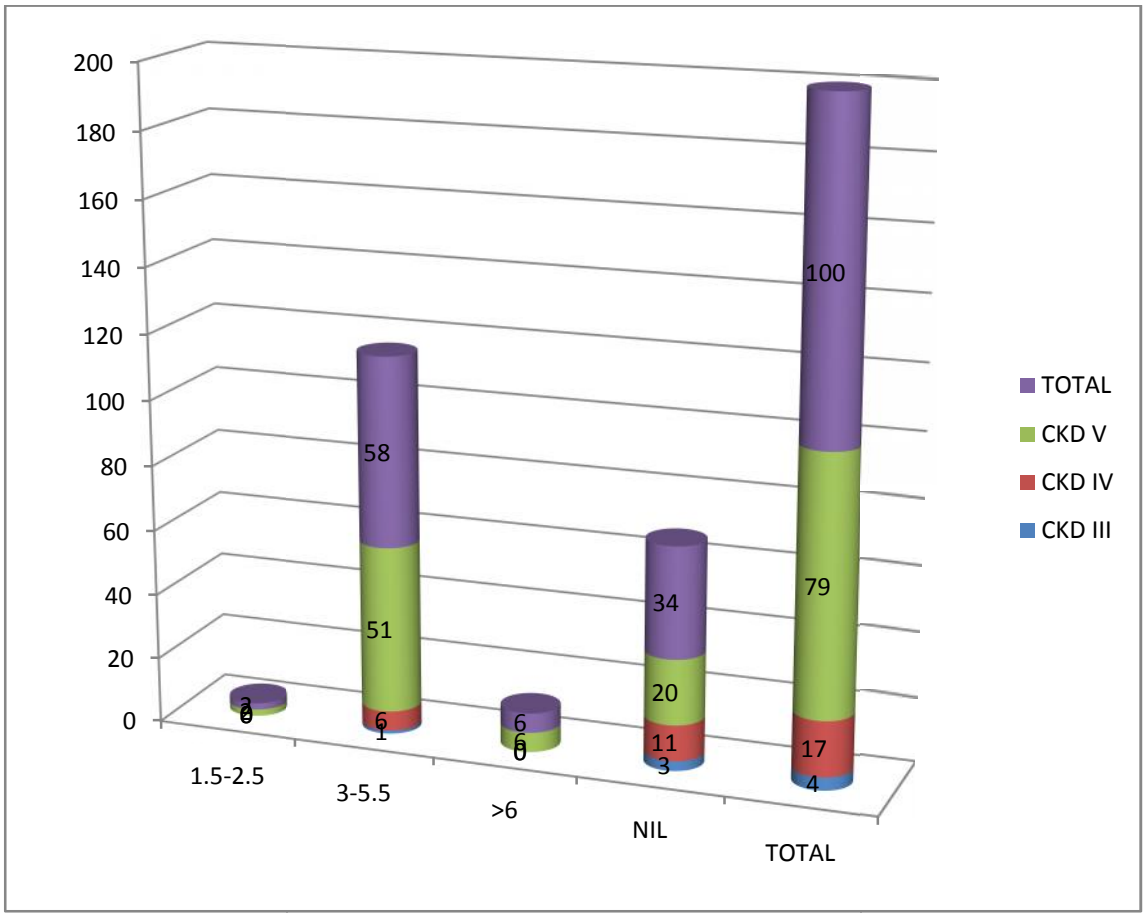
## TABLE 18: MNSI SCORES AND CKD STAGES

| MNSI SCORES | CKD STAGES | | | TOTAL |
|---|---|---|---|---|
| | III | IV | V | |
| 1.5-2.5 | 0 | 0 | 2 | 2 |
| 3-5.5 | 1 | 6 | 51 | 58 |
| 6-10 | 0 | 0 | 6 | 6 |
| 0 | 3 | 11 | 20 | 34 |
| TOTAL | 4 | 17 | 79 | 100 |

In the study group no patients from CKD stage III & IV have scored MNSI Scores ranging from 1.5-2.5 or 6-10.Two patients from CKD stage V had scored between 1.5-2.5. One patient from CKD Stage III,6 patients from CKD Stage IV and 51 patients (64.55%) from CKD Stage V has scored between 3-5.5.Six patients (7.5%) from CKD Stage V group were the sole group of patients who had scored above 6.

The distribution was statistically significant $\chi^2=13.418$ with 6 degrees of freedom with p value 0.037(<0.05)

**CHART 16:MNSI SCORE DISTRIBUTION CHART AMONG CKD SUBCLASSES**




**Diabetic neuropathic symptom score and UPN:**

The lowest DNSS score obtained was 0 and the maximum score was 3,the mean score was 0.27 with a standard deviation of 0.548.

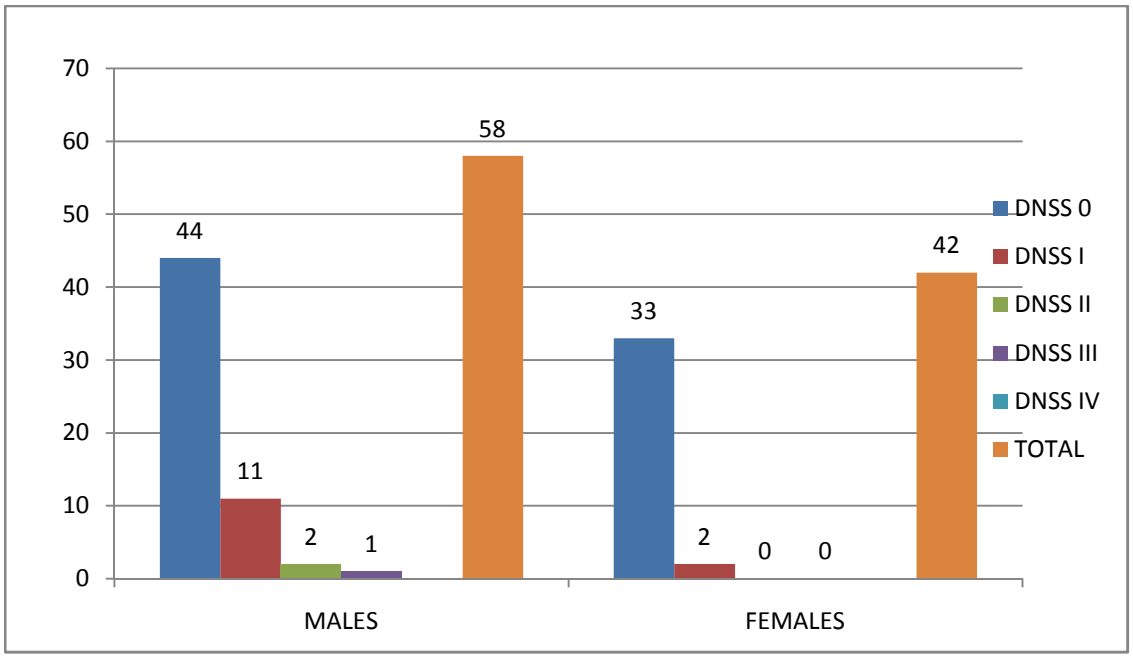
**TABLE 19:GENDER AND DNSS**

| GENDER | DNSS | | | | | TOTAL |
|---|---|---|---|---|---|---|
| | 0 | I | II | III | IV | |
| MALES | 44 | 11 | 2 | 1 | 0 | 58 |
| FEMALES | 33 | 9 | 0 | 0 | 0 | 42 |
| Total | 77 | 20 | 2 | 1 | 0 | 100 |

Out of 100 patients, 23 patients(23% prevalence) had scored 1 and above in DNSS which was statistically significant. 20 patients had scored 1 point, out of which there were 11 males (55%) and 9 females(45%).2 patients had scored 2 points out of which there were 2 males and none were females. Only one male patient had scored 3 points.

The prevalence of peripheral neuropathy according to DNSS score was statistically insignificant (p value>0.05) among genders.

## CHART 17:GENDER AND DNSS DISTRIBUTION CHART




**Age and DNSS:**

Out of 100 patients, none of the patients aged less than 30 years scored in DNSS questionnaire. Out of 60 patients who belonged to the 30-59 age group, 8 patients had scored 1 point, 1 patient has scored 2 point and another patient had scored 3 points, the prevalence of neuropathic symptoms in patient aged 30-59 was 16.66%.In patients aged 60 and above 12 patients scored 1 point and only one patient scored 2 points and none had scored 3 points. The prevalence of uremic symptoms in patients aged 60 and above was 48.14% which was statistically significant (p value <0.05), $\chi^2$=16.775 with 6 degree of freedom.

**TABLE 20:AGE& DNSS**

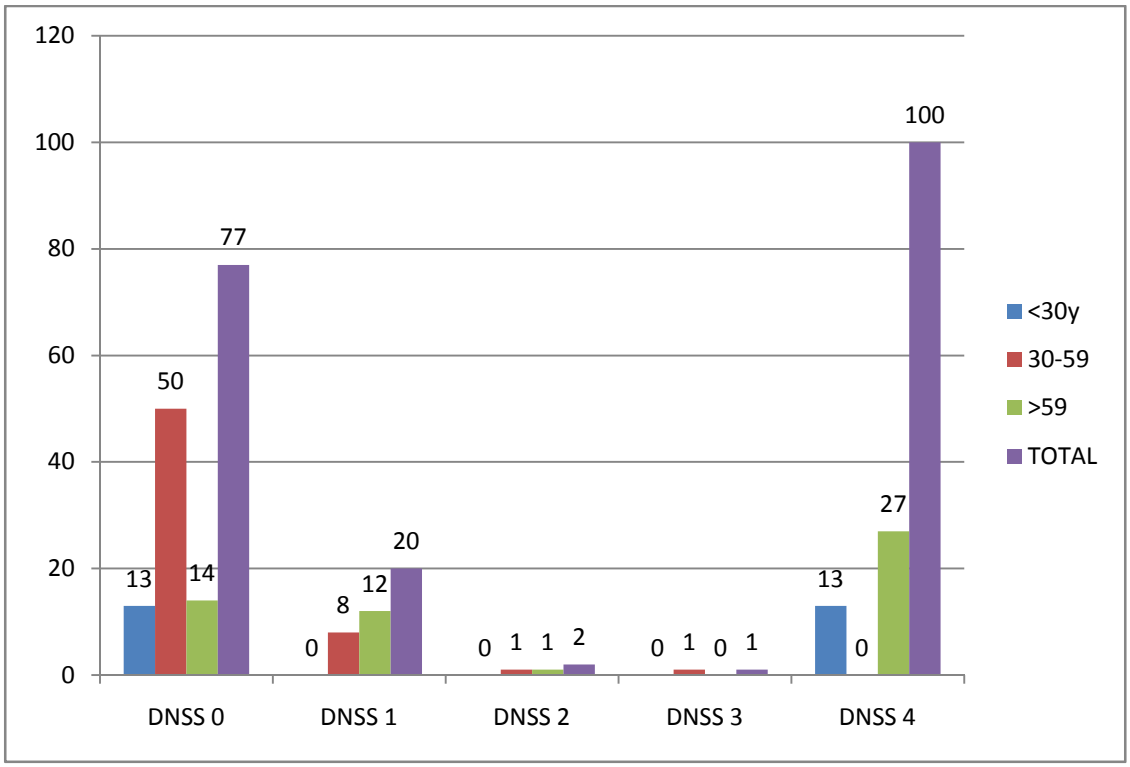
| DNSS | AGE | | | |
|---|---|---|---|---|
| | <30years | 30-59years | >59 years | |
| 0 | 13 | 50 | 14 | 77 |
| 1 | 0 | 8 | 12 | 20 |
| 2 | 0 | 1 | 1 | 2 |
| 3 | 0 | 1 | 0 | 1 |
| 4 | 0 | 0 | 0 | 0 |
| Total | 13 | 60 | 27 | 100 |

Most common symptom of uraemic neuropathy according to DNSS scores was Burning feet closely followed by numbness.Pin prick sensations and gait unsteadiness were rarer complaints.

**TABLE 21: MOST COMMON SYMPTOMS**

| S.NO | Symptoms | Total |
|---|---|---|
| 1. | Burning feet | 10(43.47%) |
| 2. | Numbness | 8(34.78%) |
| 3. | Pin prick sensation | 3(13.04%) |
| 4. | Unsteadiness of gait | 2(8.69%) |

## CHART 18: AGE AND DNSS DISTRIBUTION CHART



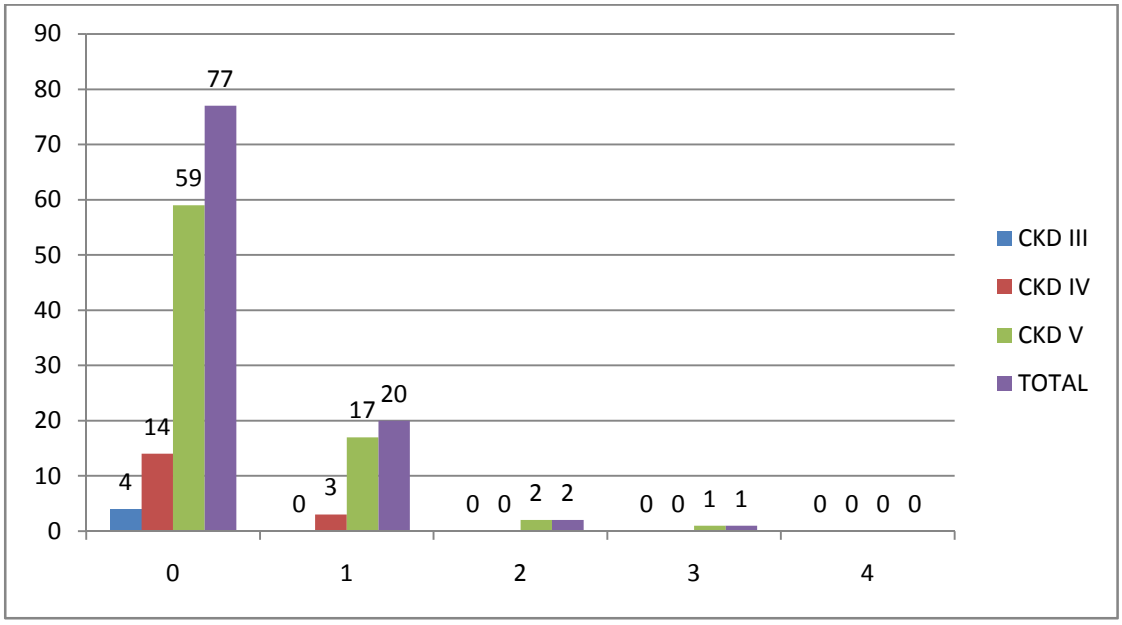

**CKD STAGE AND DNSS:**

Among 4 patients who belonged to CKD STAGE III group, none of the patients had scored any point, among 17 patient in CKD stage IV group, 3 patients scored 1 point.Among 79 patient in CKD stage V,17 patient scored 1 point,2 patient scored 2 point and 3 patient scored 1 point. The prevalence of peripheral neuropathy according to DNSS scores were 25.31% in CKD STAGE V,17.64% in CKD STAGE IV and 0% in CKD STAGE 3, which was statistically not significant (p value 0.425) with 2 degrees of freedom.

## TABLE 22:DNSS and CKD SUBCLASSES

| DNSS SCORE | CKD STAGE | | | TOTAL |
|---|---|---|---|---|
| | III | IV | V | |
| 0 | 4 | 14 | 59 | 77 |
| 1 | 0 | 3 | 17 | 20 |
| 2 | 0 | 0 | 2 | 2 |
| 3 | 0 | 0 | 1 | 1 |
| Total | 4 | 17 | 79 | 100 |

## CHART 19:DNSS AND CKD STAGE CHART



**CKD DURATION AND DNSS:**

The prevalence of peripheral neuropathy according to DNSS scores and CKD duration was not statistically significant, p value=0.550(>0.05), $\chi^2$=22.493

**eGFR and DNSS**:

The prevalence of peripheral neuropathy according to DNSS scores and eGFR was not statistically significant,p value=0.907(>0.05), with $\chi^2$=2.219 ,degree of freedom=6

**DYSLIPIDEMIA DISTRIBUTION:**

Age distribution:

Among patients aged <30y two patient had dyslipidemia (15.38%),Twenty two patients among patients aged 30-60y (36.66%) had dyslipidemia and in patients aged 60 and above 12 patients had dyslipidemia (44.44%).The distribution of dyslipidemia among patients age was not statistically significant, $\chi^2$=3.245 with 2 degree of freedom p value=0.197(>0.05)

**TABLE 23:AGE AND DYSLIPIDEMIA**

| DYSLIPIDEMIA | AGE | | | Total |
|---|---|---|---|---|
| | <30 | 30-60 | >60 | |
| YES | 2 | 22 | 12 | 65 |
| NO | 11 | 38 | 15 | 35 |
| Total | 13 | 60 | 27 | 100 |

**GENDER DISTRIBUTION:**

Among the study population, 23 males (39.65%) had dyslipidemia and 13female patients (30.95%) had dyslipidemia. The distribution of dyslipidemia among genders was not statistically significant. $\chi^2$=0.801 with 1 degree of freedom and p value was 0.371(>0.05)

**TABLE 24:GENDER AND DYSLIPIDEMIA**

| Dyslipidemia | GENDER | | Total |
|---|---|---|---|
| | MALE | FEMALE | |
| YES | 23 | 13 | 36 |
| NO | 35 | 29 | 64 |
| Total | 58 | 42 | 100 |

**DYSLIPIDEMIA IN CKD SUBSTAGES:**

Among the patients none of the stage III patients had dyslipidemia, whereas 4 patients from CKD stage 4 had dyslipidemia (23.52%).Among the CKD stage V patients 32 had dyslipidemia (40.50%).The prevalence of uremic neuropathy in CKD Stage did not have any statistical significance. $\chi^2$=4.094 with degree of freedom 2 and p value was 0.129(>0.05)

## TABLE 25:DYSLIPIDEMIA AND CKD STAGES

| DYSLIPIDEMIA | CKD STAGE | | | TOTAL |
|---|---|---|---|---|
| | III | IV | V | |
| YES | 0 | 4 | 32 | 36 |
| NO | 4 | 13 | 47 | 64 |
| Total | 4 | 17 | 79 | 100 |

**ON HD:**

Among HD patients. A total of 25 patients out of 60 patients (41.66%) had dyslipidemia and 35 patients (58,33%) did not have dyslipidemia. The distribution of dyslipidemia among HD patients was not statistically significant. $\chi^2$=2.091 with 1 degree of freedom. P value was 0.148(>0.05).

## TABLE 26:HEMODIALYSIS AND DYSLIPIDEMIA

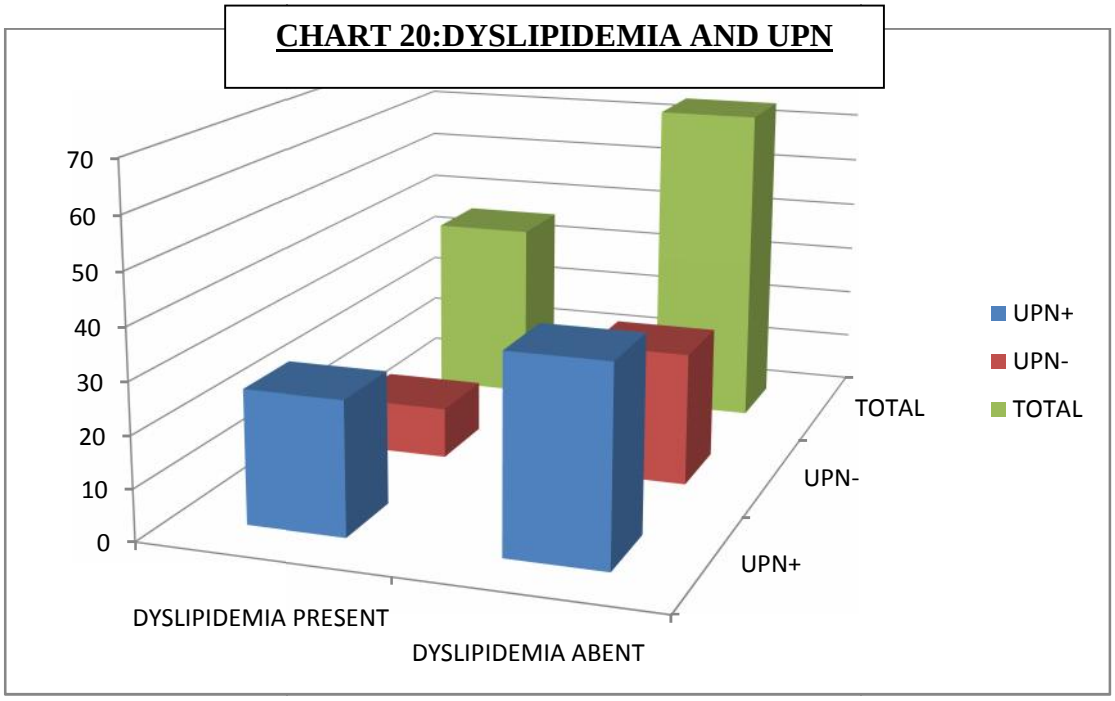
| DYSLIPIDEMIA | ON HD | | Total |
|---|---|---|---|
| | YES | NO | |
| YES | 25 | 11 | 36 |
| NO | 35 | 29 | 64 |
| TOTAL | 60 | 40 | 100 |

**UPN and Dyslipidemia:** Among patients who had dyslipidemia 26 patients(72.22%) had UPN,whereas 38 patients(59.37%) who were not dyslipidemic did not have UPN.The prevalence of UPN and dyslipidemia was not statistically significant $\chi^2$=1.651 with 1 degree of freedom.P value=0.199(>0.05)

**TABLE 27:DYSLIPIDEMIA AND UPN**

| DYSLIPIDEMIA | UPN | | Total |
|---|---|---|---|
| | YES | NO | |
| YES | 26 | 10 | 36 |
| NO | 38 | 26 | 64 |
| TOTAL | 64 | 36 | 100 |

**CHART 20:DYSLIPIDEMIA AND UPN**



**BMI and UPN:**

Among 100 patients, 2patients (50%) from the BMI group less than 19 had peripheral neuropathy and two patients did not have peripheral neuropathy. Among patients who had BMI between 19-25, Forty eight(64.86% prevalence) patients had UPN, whereas 14 patients (63.63% prevalence) who had a BMI more than 25 had UPN. This prevalence in the study group was not statistically significant. $\chi^2=0.336$ with degree of freedom 2 and the p value was 0.833(>0.05).

**TABLE 28:BMI& UPN**

| BMI | UPN | | TOTAL |
|---|---|---|---|
| | YES | NO | |
| <19 | 2 | 2 | 4 |
| 19-25 | 48 | 26 | 74 |
| >25 | 14 | 8 | 22 |
| Total | 64 | 36 | 100 |

**CHART 21:BMI and UPN**

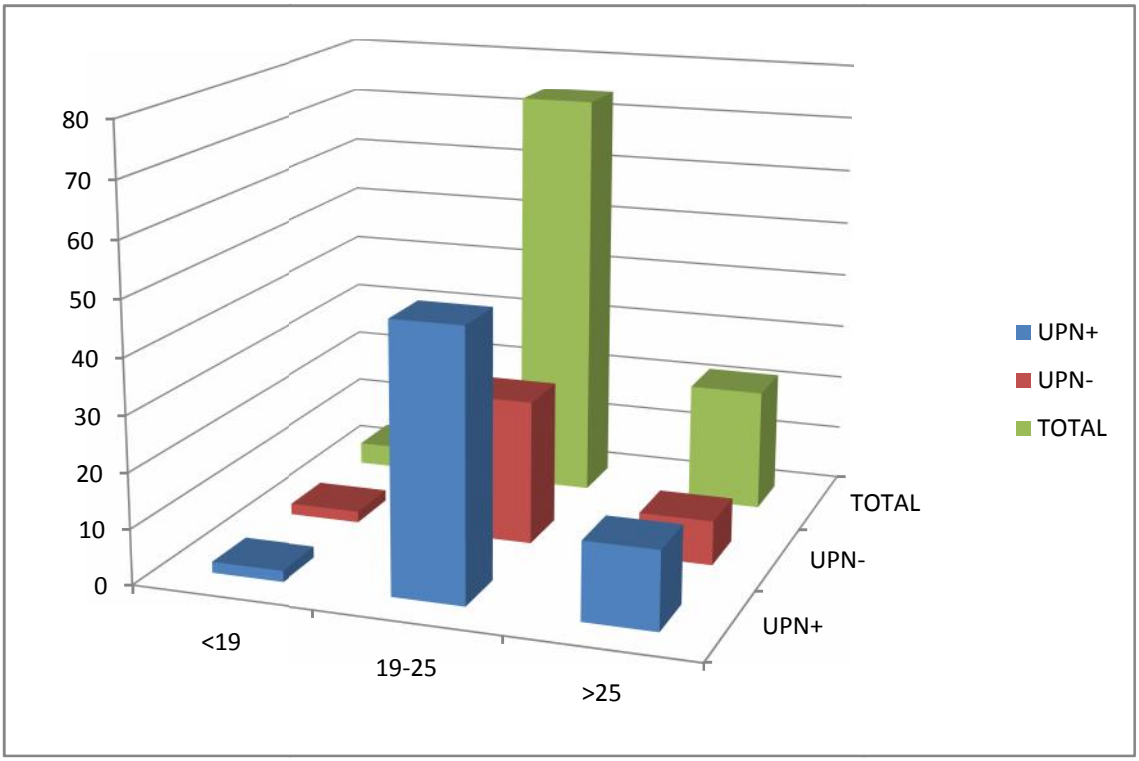



**TABLE 29: DNSS SENSITIVITY AND SPECIFICITY**

| Statistic | Formula | Value | 95% CI |
|---|---|---|---|
| Sensitivity | $\frac{a}{a+b}$ | 35.94% | 24.32% to 48.90% |
| Specificity | $\frac{d}{c+d}$ | 100.00 % | 90.26% to 100.00% |

The DNSS had a sensitivity of 35.94% and a specificity of 100%.This makes DNSS a poor screening test, hence it could not be used in early diagnosis of uremic peripheral neuropathy.

## DISCUSSION

Uremic neuropathy is the commonest complication of the uremic syndrome and is defined as a predominantly distal sensory-motor polyneuropathy that predominantly affects the distal segments more so in the lower limbs than in the upper limbs which may occasionally present as a mononeuropathy due to compression, trauma or ischemia[98,99].

The condition is often a silent burden among patients with CKD affecting the quality of life considerably. The prevalence of peripheral neuropathy due to uraemia may range from 70-100% in patients with End stage renal disease[99-103].Among the non-dialysis population,one study noted the prevalence to be 70%[104].Patients start experiencing subtle symptoms of uremic neuropathy during stage 3 CKD with peripheral neuropathy prominently affecting stage 4 and ESRD[105].

Hundred adult patients with CKD stage 3 or more were included in the present study.They were patients attending the HD ward for thrice weekly dialysis or patients admitted in the medical wards of our institution.The mean age of the study population was 47.87years with a male to female ratio of 1.38:1.

The mean duration of uremic symptoms was 28.69 months.

### AGE & GENDER:

In a study by Jedras M et al[106], conducted in 51 patients on chronic hemodialysis, more males were found to be have sensory-motor neuropathy when compared to women,whereas women were found to have more prevalent autonomic neuropathy when compared to men. Madhusudhana Babu et al in his study on 74 patients who were not on dialysis found that when compared to younger age group patients aged

more than 65years were affected by peripheral neuropathy.In his study he also noted that the prevalence of peripheral neuropathy increases among males if eGFR is <15ml/min/1.73m$^2$.

In our study males were significantly more affected by peripheral neuropathy when compared to females.This was observed in CKD stage V group(eGFR<15) both in patients on HD and in patients not on HD.This finding extended to stage IV CKD and stage III CKD groups.These findings were statistically significant in our study.

In our study it was found that patients aged ≥60 years were predominantly affected by uremic neuropathy which was statistically very significant(pvalue<0.01).

**CLINICAL-INSTRUMENTAL SCREENING TESTS FOR URAEMIC NEUROPATHY:**

Even though Nerve conduction studies are the gold standard diagnostic modality for uremic neuropathy,The nature and the lack of such facilities impedes the early diagnosis.

There are studies which claim that simple screening tools like MNSI scores and Neuropathic symptom scores which is a validated tool for diabetic neuropathy will also provide an early window of opportunity to diagnose the presence of uremic neuropathy without having to undergo nerve conduction studies which will pave way for earlier management.

**Michigan neuropathy screening instrument physical assessment (MNSI):**

Mambelli E et al[107],conducted a study on 225 dialysis patients to determine the prevalence of uremic neuropathy. In their study, all causes inducing secondary neuropathy were excluded.MNSI scores and Electroneurography of the lower limb was conducted to compare the sensory nerve conduction velocities and sensory nerve action potential results with MNSI results.37 patients(16.4%) were identified to have uremic neuropathy. There was a significant correlation between MNSI scores (>or equal to 3) between MNSI physical assessment and SCV($r^2$=0.1959;p<0.034) as well as SNAP($r^2$=0.3454;p=0.027) both measured by ENG. He concluded the study by saying that MNSI could represent a valid and simple clinical-instrumental screening test for the early diagnosis of Uremic neuropathy in view of an early therapeutic approach.

In our study of 100 patients which includes CKD patients from stage III to stage V with or without on hemodialysis. The smallest score obtained was 2 and the largest score obtained was 7 with a mean score of 2.580±2.069. two patients(2%) have scored MNSI scores between < 2.5 out of 10 and 58 patients(58%) had scored between 3-5.5 out of 10.

Further breaking down,1 patient(25% prevalence ) from CKD stage III had scored >3 in MNSI, six patient(35.29% prevalence) has scored >3 in MNSI. Finally among the CKD Stage V patients, 51 patients (64.55%) have scored >3 in MNSI.

Among the CKD V patients on HD ,43 patients(71.66% prevalence) had MNSI scores more than 3 and among CKD V patients not on HD 14 patients( 73.68%) had MNSI scores >3.

The distribution of MNSI scores among different CKD subtype was statistically significant($\chi^2$=13.418 ,$p<0.05$).Our study reiterates the fact that MNSI could serve as a valid test to diagnose Uremic neuropathy with the view that early management may have a positive impact on the quality of life of the patient.

**DNSS SCORES:**

In a study by HK Aggarwal et al[108] on 100 predialysis patients ,70% of patients had scored atleast 1 point in the T-Neuropathy symptom score with maximum score of 17[109-111].The scores were found to correlate well with the increase in levels of serum creatinine[107].

Krishnan et al. in their study on 12 ESRD patients graded the neuropathic symptoms using modified NSS. Each symptom received a score of 1, and the number of symptoms present in each subset was summed to give a T-NSS. The maximum possible T-NSS was 9. All 12 patients reported symptoms of neuropathy (mean T-NSS, 1.9±0.2) [110].

Majority of the patients had at least one neurological symptom (70%), as compared against the minority (30%) who were asymptomatic. 49% of the patients had a T-NSS of ≥2 while maximum score of 5 was elicited in 9% of the patients (mean T-NSS, 1.72±1.61).

Laaksonen et al. staged the clinical severity of uremic neuropathy in 21 CKD patients, using a modified version of the NSS and combined this assessment with results of nerve conduction studies. The neuropathy symptoms were evaluated using a modified version of the NSS developed by Dyck. Symptomatic neuropathy (T-NSS ≥2) was observed in 13 patients among the study group (61%)[112].

In our study, We have used a more simplified scoring system, the diabetic neuropathy symptom score (DNSS) assessing pain, numbness, tingling and ataxia.The maximum score of DNS is four points, one point or more indicates neurological abnormalities[113].With this scoring system we observed that the prevalence of neuropathy was 0% in stage III, 17% in stage IV and 25.31% in Stage V.This distribution was statistically insignificant($p>0.05$).

The lowest DNSS score obtained was 0 and the maximum score was 3,the mean score was $0.27\pm0.548$.

The distribution of DNSS scores and Serum creatinine levels, eGFR levels and duration of CKD symptoms were statistically insignificant(p value>0.05).Thus our study concludes that oversimplified symptom scoring systems such as DNSS might not the best tool for diagnosing uremic neuropathy.T-NSS score and modified NSS score though laborious might be considered as an effective tool in screening uremic neuropathy.

## CLINICAL MANIFESTATIONS

### Symptoms:

Tyler in his study found that burning feet akin to alcoholic peripheral neuropathy are the earliest manifestation in uremic neuropathy[114],whereas Neilson in his study on 109 patients found that only 7 patients complained of burning feet.Patients with uremic polyneuropathy initially present with sensory symptoms involving the distal aspect of the lower extremities. Early sensory symptoms include paraesthesia such as tingling or prickling. Burning pain develops as neuropathy becomes more severe.

In our study,out of 100 patients only 23 patients(23%) complained of having any neurological symptom. The most common symptom was burning feet(43.47%),the least common symptom was unsteadiness of gait(8.6%).

**Signs:**

Al-Hayk and Bertorini,[115] stated that earliest findings of uremic neuropathy are loss of Achilles reflex and increased vibrating sensation threshold. Several other studies concluded that paired vibratory sense in the lower limbs and loss of deep tendon reflexes, first ankle jerks and then knee jerks, are the usual first signs of peripheral neuropathy. In comparison to sensory, the distal motor sensory neuropathy was the common type with chronic kidney disease[116].

In our study, the most frequent sign observed was absent ankle reflex (40.20%) which is consistent with the predominant large fibre involvement in uremic neuropathy,the next common sign was abnormal monofilament test(34.02%) and absent vibration perception (21.64%).

## PREVALENCE OF URAEMIC PERIPHERAL NEUROPATHY IN CKDPATIENTS

The prevalence of uremic neuropathy is 60%-100% of patients on dialysis[99-103,116]. Neuropathy generally only develops at glomerular filtration rates of less than 12 ml/min/1.73$^2$BSA [116].Aggarwal HK et al[104],in their study on 100 non dialysis patients, the prevalence was found to be 70%.

In our study, the prevalence of clinical uremic peripheral neuropathy among 100 CKD patients was 64%.After a subgroup analysis, the prevalence is as follows, In stage III CKD patients the prevalence of clinical uremic peripheral neuropathy was

25%In stage IV CKD patients the prevalence of clinical uremic peripheral neuropathy was 35.29%

Our study confirms the finding that manifestation of signs and symptoms of uremic neuropathy is not restricted to patients with eGFR<12ml/min and probably occurs much earlier. In Stage V CKD patients the prevalence of clinical uremic neuropathy was 72.15%.Which includes both Pre-dialysis and on dialysis patients.

In stage V CKD(non-Dialysis) patients the prevalence of clinical uremic peripheral neuropathy was 73.68%.The distribution of peripheral neuropathy among different CKD subclasses was statistically significant.Confirming the findings in other studies[116].

In stage V CKD(on HD)patients the prevalence of clinical uremic peripheral neuropathy was 71.6%.which was clinically and statistically significant.The course of neuropathy is variable in patients undergoing dialysis. Routine hemodialysis have found not to improve neuropathy in patients with CKD despite decrease in urea and creatinine levels,this was emphasised by many workers.[117,118] Lengthening the time on dialysis/week (more "square meter hours" i.e. ,membrane area multiplied by dialysis time) prevents neuropathy.Despite elevated urea and creatinine levels Peritoneal dialysis improves peripheral neuropathy better than hemodialysis.

These findings correlate with the observations of Asbury,that, in the past decades, the occurrence of clinically evident neuropathy in patients on chronic dialysis programme (both haemodialysis and peritoneal dialysis) has become rare, as a result of earlier institution of treatment, frequent dialysis scheduling and improvement in dialysis techniques[119,120]

**DURATION OF URAEMIC SYMPTOMS**

Madhusudhana et al, in his study found that prevalence of peripheral neuropathy increase with long duration of symptoms.

In our study the prevalence was 80% in patients with duration of symptoms more than 3 years.The prevalence of uremic peripheral neuropathy was more in patients with longer duration of uremic symptoms.

**SERUM CRETININE:**

H K Aggarwal et al,in their study on 100 patients found that prevalence of peripheral neuropathy increased with a raise in serum creatinine, This observation was confirmed in other studies as well[108,111,112,116,121].

In our study, The minmum serum creatinine observed was 1.7mgs% and the maximum was 11.3mgs% and a mean creatinine value of 5.33mgs%.The prevalence was 66% in patients with serum creatinine 6.1 to 9mgs% and in patients with serum creatinine ≥9.1 the prevalence was 100%($p<0.05$).

**DYSLIPIDEMIA:**

CKD leads to a down regulation of lipoprotein lipase and the LDL-receptor, and increased triglycerides in CKD are due to delayed catabolism of triglyceride rich lipoproteins, with no differences in production rate[122]. CKD is associated with lower levels of apoA-I (due to decreased hepatic expression and higher apoB/apoA-I. Decreased lecithin-cholesterol acyltransferase (LCAT) activity and increased cholesteryl ester transfer protein (CETP) activity contribute to decreased HDL-

cholesterol levels. Beyond decreased HDL cholesterol levels, the HDL in CKD is less effective in its anti-oxidative and anti-inflammatory functions

As CKD progresses the dyslipidemia often worsens. In an evaluation of 2001-2010 National Health and Nutrition Examination Survey (NHANES), the prevalence of dyslipidemia increased from 45.5% in CKD stage 1 to 67.8% in CKD stage 4; similarly, the use of lipid lowering agents increased from 18.1% in CKD stage 1 to 44.7% in CKD stage 4[123] Of more than 1000 hemodialysis patients studied only 20% had "normal" lipid levels (defined as LDL<130 mg/dl, HDL > 40 and triglycerides < 150); of 317 peritoneal dialysis patients only 15% had "normal" lipid levels[124]. A larger study evaluating dyslipidemia in > 21,000 incident dialysis patients found 82% prevalence of dyslipidemia

In our study the prevalence of dyslipidemia was 0% in stage III, 23.5% in stage IV and 40.5% in stage V CKD. None of these findings were statistically significant.

## LIMITATIONS OF THIS STUDY

1.The long mean duration of uremic symptoms in our patients was probably due to 'Recall bias'.

2.The positive correlation between MNSI and Electroneuronography as seen by Mambelli et al, was observed in Italians.There are no reference studies done in Asian or in any other population groups. Further studies need to be done on different population subgroups in future.

## CONCLUSION

1) The prevalence of clinical uremic peripheral neuropathy in a series of 100 chronic kidney disease patients which includes different stages of CKD ranging from stage 3 to stage 5 CKD including those on hemodialysis was **64%**.

2)The prevalence of peripheral neuropathy in various subgroups of CKD stages were **25%** in stage III CKD ,**35.29%** in stage IV CKD and **64.55%** in stage V CKD.

3)Patients on Hemodialysis had a prevalence of **71.77%**,whereas patients not on hemodialysis who belonged to CKD stage 5group had a prevalence of **73.68%**.

4)Clinical neuropathy occurred more commonly in males,older age groups(>60years), patients with longer duration of uraemic symptoms, elevated serum creatinine levels and decreasing eGFR levels.

5)The most common symptom was burning foot and the most common clinical sign observed was loss of ankle reflex.

Prevalence of uremic neuropathy is high in patients with CKD.Since this condition occurs even in patients not requiring dialysis and worsens with increasing duration of symptoms, our study emphasises the need for active screening of uremic peripheral neuropathy in patients with CKD with simple diagnostic tools like MNSI so that early institution of treatment and further management may play a positive role in the life of CKD patients.

# BIBLIOGRAPHY

1. Asbury AK, Victor M, Adams RD. Uremic polyneuropathy. Arch Neurol Psychiatr .1963;8:413–428.

2. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. Clin Neurol Neurosurg. 2004;107:1–16.

3. Bragmann JM, Skorecki K: Chronic Kidney Disease. In: Harrison's Principle's of Internal Medicine 17th edition, Vol 2, Mcgraw Hill 2008;1761-1763.

4. Dash SC, Agarwal SK. Incidence of chronic kidney disease in India.Nephrology DialysisTransplantation.2006;21:232-3.

5. Modi GK, Jha V. The incidence of end-stage renal disease in India: A population-based study. International Society of Nephrology 2006;70;21:31-3.

6. Charcot JM. Leconssur les maladies du systemenerveux. XVI Desparaplegies urinares.3rd ed.Paris:1880:295.

7. Dyck NJ. Segmental demyelination secondary to axonal degeneration inuremic neuropathy.MayoClinicProceedings1971;46:400.

8. Douglas W. Zochodne: Uremic neuropathy. In: Dyck PJ, Thomas PK, Lambert IM eds. Peripheral neuropathy 4th Edition, Vol 2, W.B Sunders and Co. 2005;982-92.

9. Neilson VK. The peripheral nerve function in CRF. VI- The relationshipbetween sensory and motor conduction and kidney function, azotemia, age, sex and clinical neuropathy.ActaMedicaScandinavica1973:194:455

10. Bolton CF, Young GB. Neurological Complications of Renal Disease. Stoneham, Mass: Butterworth-Heinemann;1990:1-256.

11. Raskin NH, Fishman RA. Neurological disorders in renal failure. NewEngland Journal of Medicine. 1976;294:204.

12. Scribner BH, Farrell PC, Milutinovic J: Evolution of the middle molecular hypothesis. Proc 5th IntCongr Nephrol (Mexico*)* 1972;5:190.

13 Man NK: An approach to "middle molecules" identification in artificial kidney dialysate, with reference to neuropathy prevention. Trans Am Soc Artif Intern Organs1973;19:320.

14. Bergstrom .J, Furst P: Uremic toxins. In: Drukker W, Parsons FM, Maher JF, ed. Replacement of Renal Functionby Dialysis, Boston: Martinus Nijhoff Publishers; 1983:354-377

15. Vanholder R: Low molecular weight uremic toxins. In: Ronco C, Bellomo R, ed. Critical Care Nephrology, Hingham,MA: Kluwer Academic Publishers; 1998:855-868.

16. Vanholder R: Pathogenesis of uremic toxicity. In: Ronco C, Bellomo R, ed. Critical Care Nephrology, Hingham, MA: Kluwer Academic Publishers; 1998:845-853.

17. Miyata T, Kirokawa K, van Ypersele de Strihou C: Relevance ofoxidative and carbonyl stress to long-term uremic complications. KidneyInt 2000;58:120-S125

18. Kielstein JT, Zoccali C: Asymmetric dimethylarginine: A cardiovascularrisk factor and a uremic toxin coming of age?. Am J KidneyDis 2005;46:186-202.

19. Horl WH: Atherosclerosis and uremic retention solutes. KidneyInt 2004; 66:1719-31.

20. Bolton CF. Peripheral neuropathies associated with chronic renalfailure. Can J Neurol Sci.May1980;7:89-96.

21. Bolton CF. Chronic dialysis for uremia. N Engl J Med.Mar 27 1980;302:755.

22. Giovannetti S, Balestri PL, Barsotti G: Methylguanidine in uremia. ArchIntern Med1973;131:709.

23. De Deyn PP, Marescau B, D'Hodge R, et al: Guanidino compound levels in brain regions of non-dialyzed uremic patients. NeurochemInt 1995;27:227-37

24. De Deyn PP, D'Hooge R, Van Bogaert P, Marescau B: Endogenous guanidino compounds as uremic neurotoxins. Kidney Int 2002;59:77-S83

25. Faden AI, Demediuk P, Panter SS, Vink R: The role of excitatory amino acids and NMDA receptors in traumatic brain injury.Science 1989;244:798-800.

26. Lipton SA, Rosenberg PA: Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 1994;330:613-22.

27. Beal MF: Mechanisms of excitotoxicity in neurologic disease. FASEBJ 1992;6:3338-44.

28. Davidoff F: Guanidine derivatives in medicine. N Engl JMed 1973;289:141-6.

29. Murray AM, Tupper DE, Knopman DS, et al: Cognitive impairment inhemodialysis patients is common. Neurol 2006;67:216-23.

30. Dhondt A, Vanholder R, van Beisen W, Lameire N: The removal of uremic toxins. Kidney Int 2000;58:47-59.

31. Asahi K, Ichimori K, Nakaawa H, Izuhara Y: Nitric oxide inhibits the formation of advanced glycation end products. Kidney Int 2000;58:1780-87.

32. Cohen H, Rdnicki M, Horl WH: Uremic toxins modulate the spontaneous apoptotic cell death and essential functions of neutrophils.Kidney Int 2001; 59:48-52

33. Garg PP, Frick KD, Diener-West M, Powe NR: Effect of the ownership of dialysis facilities on patients' survival and referral for transplantation. NEngl J Med 1999; 341:1653-60

34 Wanner C, Zimmermann J, Schwedler S, Metzger T: Inflammation and cardiovascular risk in dialysis patients. Kidney Int 2002;61:99-102.

35. Meeus F, Kourilsky O, Guerin AP, et al: Pathophysiology of cardiovascular disease in hemodialysis patients. Kidney Int 2000;58:140-7

36. Makita Z, Radoff S, Rayfield EJ, et al: Advanced glycosylation end products in patients with diabetic nephropathy. N Engl JMed 1991;325:836-42.

37. Haag-Weber M: AGE-modified proteins in renal failure. In: Ronco C, Bellomo R, ed. Critical Care Nephrology, Hingham,MA: Kluwer Academic Publishers;1998:878-83.

38 Miyata T, Van Ypersele de Strihou C, Ueda Y, et al: Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: Biochemical mechanisms. J Am SocNephrol 2002;13:2478-87.

39. Koenig H, Goldstone AD, Lu CY, Trout JJ: Polyamines: Transducers of osmotic signals at the blood-brain barrier. Proc Am SocNeurochem 1988;19:79

40. Fraser CL, Arieff AI: Nervous system manifestations of renal failure. In: Schrier RW, Gottschalk CW, ed. Diseases of the Kidney, 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2001:2769-94**.**

41. Moe SM, Sprague SM: Uremic encephalopathy. ClinNephrol 1994;42:251-6.

42. Cooper JD, Lazarowitz VC, Arieff AI: Neurodiagnostic abnormalities in patients with acute renal failure. Evidence for neurotoxicity of parathyroidhormone. J Clin Invest1978;61:1448-55.

43. Cogan MG, Covey C, Arieff AI, et al: Central nervous system manifestations of hyperparathyroidism. Am J Med 1978;65:963-70.

44. Guisado R, Arieff AI, Massry SG, et al: Changes in theelectroencephalogram in acute uremia. Effects of parathyroid hormone andbrain electrolytes. J Clin Invest 1975;55:738-45.

45. Mahoney CA, Arieff AI, Leach WJ, Lazarowitz VC: Central andperipheral nervous system effects of chronic renal failure. KidneyInt 1983;24:170-7.

46. Arieff AI, Massry SG: Calcium metabolism of brain in acute renal failure. Effects of uremia, hemodialysis, and parathyroid hormone. J ClinInvest 1974; 53:387-92.

47. Akmal M, Goldstein DA, Multani S, Massry SG: Role of uremia, brain calcium and parathyroid hormone on changes in electroencephalogram in chronic renal failure. Am J Physiol 1984; 246:575-9.

48. De Boer IH, Gorodetskaya I, Young B, et al: The severity of secondary hyperparathyroidism in chronic renal insufficiency is GRF-dependent, race dependent, and associated with cardiovascular disease. J Am SocNephrol 2002;13:2762-9.

49. Sato Y, Kaji M, Metoki N, et al: Does compensatoryhyperparathyroidism predispose to ischemic stroke? Neurol 2003;60:626–9.

50. Gatewood JW, Organ CH, Mead BT: Mental changes associated withhyperparathyroidism. Psychiatry 1975;123:129.

51. Heath H, Hodgson SF, Kennedy MA: Primary hyperparathyroidism: Incidence, morbidity, and potential impact in a community hospital. N EnglJ Med 1980; 302:189-93.

52. Luxenberg J, Feigenbaum LZ, Aron JM: Reversible long-standing dementia with normocalcemic hyperparathyroidism. J Am GeriatrSoc1984;32:546-7.

53. Fraser CL, Arieff AI: Hepatic encephalopathy. N Engl JMed 1985; 313:865-73.

54. Goldstein DA, Massry SG: The relationship between the abnormalities in EEG and blood levels of parathyroid hormone in dialysis patients. J ClinEndocrinolMetab 1980;51:130.

55. Mahoney CA, Arieff AI: Uremic encephalopathies: Clinical, biochemical and experimental features. Am J Kidney Dis 1982;2:324-36.

56. Rasmussen H, Goodman DBP: Relationships between calcium and cyclic nucleotides in cell activation: Cellular calcium metabolism and calcium-mediated cellular processes. Physiol Rev 1977;57:428

57. Braguer D, Gallice P, Yatzidis H, et al. Restoration by biotin of the in vitro microtubule formation inhibited by uremictoxins. Nephron. 1991;57:192-6.

58. Danziger CH. Uremic neuropathy and treatment with renal transplantation. ANNA J. Apr 1989;16:67-70.

59. Dhondt A, Vanholder R, Van Biesen W, et al. The removal of uremictoxins. Kidney Int. 2000;76:47-59.

60. Fraser CL, Arieff A. Nervous system complication of uremia. Annals ofInternal Medicine.1988;109:143.

61. Neilson VK. The peripheral nerve functions in CRF. V – Sensory and motor conduction velocity. ActaMedicaScandinavica 1973;194:445.

62. Thomas PK. The polyneuropathy of chronic renal failure. Brain 1971; 94:761.

63. Tyler HR. Neurologic disorders in renal failure. American Journal of Medicine.1968;44:734.

64. Spencer PS, Schaumberg HH: Central peripheral distal axonopathy—The pathology of “dying-back” polyneuropathies. ProgNeuropathol 1977;3:255.

65. Nielsen VK: The peripheral nerve function in chronic renal failure. VI.Acta Med Scand 1973;194:455.

66. Thomas PK, Hollinrake K, Lascelles RG: The polyneuropathy of chronicrenal failure. Brain1971;94:761.

67. Spencer PS, Sabri MI, Schaumberg HH: Does a defect of energy metabolism in the nerve fiber underlie axonal degeneration inpolyneuropathies?. Ann Neurol 1979;5:501.

68. Calcutt NA, Allendoerfer KL, Mizisin AP, Middlemas A: Therapeutic efficacy of sonic hedgehog protein in experimental diabetic neuropathy. JClin Invest 2003; 111:507-14.

69. Campistol JM: Uremic myopathy. Kidney Int 2002;62:1901-13.

70. Tyler HR: Neurologic disorders seen in the uremic patient. Arch InternMed 1970; 126:781-6.

71. Robinson TG, Carr SJ: Cardiovascular autonomic dysfunction in uremia.Kidney Int 2002;62:1921-32

72. Abella R. Periodic dialysis in terminal uremia. JAMA 1967;199:362.

73. Dinapoli R. Experience with combined hemodialyisis renal transplant programme- Neurological Aspects. Mayo Clinics Proceedings 1966;41:804

74. Pendras JP. Hemodialysis - a successful therapy. Annals of Internalmedicine 1966;64:293

75. Shupak E. Experience with long term intermittent haemodialysis. Annalsof Internal medicine1965;62:509.

76. Woywodt A, Meier M, Kaiser D, Schneider G, Haller H, Hiss.M. Incenterintermittent peritoneal dialysis: retrospective ten-year single-centerexperience with thirty consecutive patients. Peritoneal Dialysis International.2008;28:518-26

77. John T. Daugirdas et al, in Handbook of dialysis, Fourth edition 2007,LW& W: 390-391

78. D. Jurcic et al.: Uremic Neuropathy in Long-Term Hemodialysis, Coll.Antropol. 32 2008;3:771–5.

79. Coomes EN, Berlyme GM, ProcEur Dial TransplAssoc, 1965;133.-40.

80.Desmedt JE. New developments in electromyography and clinical neurophysiology.New York, S. Karger; 1973.

81. Konotey -Ahulu FIet al, Br Med J, 2 (1965) 1212. -20**.**

82. Caccia MR, Mangilla, Mecca G, UbialiE, J Neurol, 1997;217:123-8.

83. Bolton CF, Baltzan MA. Baltzan RB. Effects of renal transplantation on uremic neuropathy.Acta Med Scand 1974;284:1170-5.

84. Nielsen K. The peripheralnerve function in chronic renal failure. IX: Recovery after renal transplantation electrophyiological aspects (sensory and motor nerve conduction). ActaMedScand 1974;195:171-80.

85. Presvick G. Subclinical polyneuropathy in clinical renal insufficiency.Lancet 1964;2:731

86. Jebsen RH. Natural history of uremic peripheral neuropathy and the effects of dialysis. New England Journal of Medicine 1967;277:327.

87. Clements RSJ, DeJesus PVJ, Winegrad AI: Raised plasma-myoinositol levels in uraemia and experimental neuropathy. Lancet 1973;1:1137-41.

88. Goldstein DA, Chui LA, Massry SG: Effect of parathyroid hormone and uremia on peripheral nerve calcium and motor nerve conduction velocity. JClin

Invest1978;62:88-92.

89. Locke SJ, Merrill JP, Tyler HR: Neurological complications of acuteuremia. Arch Intern Med.1961;108:519-30.

90. Arieff AI: Neurological complications of renal insufficiency. In: Brenner BM, ed. Brenner & Rector's The Kidney, 7th ed.Philadelphia: WB Saunders; 2004:2227-54.

91. .Lonergan ET, Semar M, Sterzel RB, et al: Erythrocyte transketolaseactivity in dialyzed patients. N Engl J Med 1971;284:1399.

92. Reznek RH, Salway JG, Thomas PK: Plasma myoinositol concentrations in uraemic neuropathy. Lancet 1977;1:675.

93. Mallette LE, Pattern BM, Engle WK: Neuromuscular disease in secondary hyperparathyroidism. Ann Intern Med 1975;82:474.

94. McQuillen MP, Gorin FJ: Serial ulnar nerve conduction velocity measurements in normal subjects. J NeurolNeurosurgPsychiatry 1969;32:144.

95. Lachman T. Late responses on aids to diagnosis in peripheral neuropathy. Journal of Neurology, Neurosurgery and Psychiatry 1980:43:156.

96. Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. Muscle & nerve. 2007 Mar 1;35(3):273-90**.**

97. Jurcić D, Bago J, Eljuga D, Milutinović S, Bobinac A, Bakula V, Bilić A. Features of uremic neuropathy in long-term dialysis. Collegium antropologicum. 1998 Jun;22:119-25.

98. Fraser CL, Arieff AI (1988). Nervous system complications in uremia. Ann. Intern. Med., 109:143-53.

99. Bolton CF. Peripheral Neurophathies Associated With Chronic Renal Failure. Canadian Journal of Neurological Sciences. 1980 May;7:89-96.

100.Laaksonen S, Metsärinne K, Voipio-Pulkki LM, Falck B. Neurophysiologic parameters and symptoms in chronic renal failure. Muscle & nerve. 2002 Jun 1;25:884-90.

101. Tilki HE, Akpolat T, Coşkun M, Stålberg E. Clinical and electrophysiologic findings in dialysis patients. Journal of Electromyography and Kinesiology. 2009;19:500-8.

102. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. Brain. 2005;128:2164-74.

103. Angus-Leppan H, Burke D. The function of large and small nerve fibers in renal failure.Muscle & nerve. 1992 Mar 1;15:288-94.

104.Aggarwal HK, Sood S, Jain D, et al. Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Ren Fail. 2013;35:1323.

105.Bragmann JM, Skorecki K: Chronic Kidney Disease. In: Harrison's Principle's of Internal Medicine 19th edition, Vol 2,1818-19.

106.Jedras M, Zakrzewska-Pniewska B, Wardyn K, Switalski M. Uremic neuropathy--I. Is uremic neuropathy related to patient age, duration of nephropathy and dialysis treatment?.PolskieArchiwumMedycynyWewnetrznej. 1998;99:452-61.

107. Mambelli E, Barrella M, Facchini MG, Mancini E, Sicuso C, Bainotti S, Formica M, Santoro A. The prevalence of peripheral neuropathy in hemodialysis patients.Clinical nephrology. 2012;77:468-75.

108.Aggarwal HK, Sood S, Jain D, Kaverappa V, Yadav S. Evaluation of spectrum of peripheral neuropathy in predialysis patients with chronic kidney disease. Renal failure. 2013;35:1323-9.

109. Dyck PJ, Sherman WR, Hallcher LM, John Service F, O'Brien PC, Grina LA, Palumbo PJ, Swanson CJ. Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry. Annals of neurology.1980 Dec 1;8:590-6.

110. Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. Muscle & nerve. 1988 Jan 1;11:21-32.

111.Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Kiernan MC. Sensory nerve excitability and neuropathy in end stage kidney disease. J NeurolNeuroSurg Psychiatry. 2006;77:548–51

112.Laaksonen S, Metsarinne K, Voipio-Pulkki LM, Falck B. Neurophysiologic parameters and symptoms in chronic renal failure. Muscle Nerve. 2002;25:884–90.

113.Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Diabetic Medicine 2002;19:962-5.

114.Tyler HR. Neurologic disorders in renal failure. American Journal of Medicine. 1968;44:734.

115. Al-Hayk K, Bertorini TE. Neuromuscular complications in uremics: a review. The neurologist. 2007;13:188-96.

116. Krishnan AV, Kiernan MC. Uremic neuropathy: clinical features and new pathophysiological insights. Muscle & nerve. 2007;35:273-90.

117.Tyler HR. Neurologic disorders in renal failure. American Journal of Medicine. 1968;44:734.

118. Neilson VK. The peripheral nerve functions in CRF. V – Sensory and motor conduction velocity. ActaMedicaScandinavica 1973;194:445

119.Manis T, Friedman EA. Dialytic therapy for irreversible uremia. New England Journal Of Medicine 1979;309:1260-321.

120.Douglas W. Zochodne: Uremic neuropathy. In: Dyck PJ, Thomas PK, Lambert IM eds. Peripheral neuropathy 4th Edition, Vol 2, W.B Sunders and Co. 2005;982-92.

121. Tilki HE, Akpolat T, Coşkun M, Stålberg E. Clinical and electrophysiologic findings in dialysis patients. Journal of Electromyography and Kinesiology. 2009;19:500-8.

122. Chan, D. T., G. K. Dogra, A. B. Irish, E. M. Ooi, P. H. Barrett, D. C. Chan, and G. F. Watts. 2009. Chronic kidney disease delays VLDL-apoB-100 particle catabolism: potential role of apolipoprotein C-III. J Lipid Res50: 2524-31.

123.Kuznik, A., J. Mardekian, and L. Tarasenko. 2013. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001-2010. BMC nephrology 14:132.

124. Longenecker, J. C., J. Coresh, N. R. Powe, A. S. Levey, N. E. Fink, A. Martin, and M. J. Klag. 2002. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am SocNephrol 13: 1918-27.

# PROFORMA

- **NAME :**
- **AGE :**
- **SEX :**
- **OCCUPATION :**
- **ADDRESS :**
- **IP/OP NO. :**
- **CBC :**
- **PERIPHERAL SMEAR :**
- **RFT :**
- **RBS :**
- **LFT :**
- **TSH :**
- **LIPID PROFILE :**
- **ECG :**
- **USG ABDOMEN :**
- **CT ABDOMEN (if needed) :**
- **BP :**
- **HEIGHT :**

- **WEIGHT :**
- **BMI :**
- **WAIST CIRCUMFERENCE :**
- **DURATION OF URAEMIA :**
- **ON HEMODIALYSIS (Y/N) :**
- **IF YES DURATION OF HD :**
- **ALCOHOLIC :** ☐ **YES** ☐ **NO**
- **eGFR by MDRD FORMULA :**
- **STAGE OF CKD :**

## MICHIGAN NEUROPATHY SCREENING INSTRUMENT

**A. History** (To be completed by the person with diabetes)

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check yes or no based on how you usually feel. Thank you.

| | | |
|---|---|---|
| 1. Are you legs and/or feet numb? | ☐ Yes | ☐ No |
| 2. Do you ever have any burning pain in your legs and/or feet? | ☐ Yes | ☐ No |
| 3. Are your feet too sensitive to touch? | ☐ Yes | ☐ No |
| 4. Do you get muscle cramps in your legs and/or feet? | ☐ Yes | ☐ No |
| 5. Do you ever have any prickling feelings in your legs or feet? | ☐ Yes | ☐ No |
| 6. Does it hurt when the bed covers touch your skin? | ☐ Yes | ☐ No |
| 7. When you get into the tub or shower, are you able to tell the hot water from the cold water? | ☐ Yes | ☐ No |
| 8. Have you ever had an open sore on your foot? | ☐ Yes | ☐ No |
| 9. Has your doctor ever told you that you have diabetic neuropathy? | ☐ Yes | ☐ No |
| 10. Do you feel weak all over most of the time? | ☐ Yes | ☐ No |
| 11. Are your symptoms worse at night? | ☐ Yes | ☐ No |
| 12. Do your legs hurt when you walk? | ☐ Yes | ☐ No |
| 13. Are you able to sense your feet when you walk? | ☐ Yes | ☐ No |
| 14. Is the skin on your feet so dry that it cracks open? | ☐ Yes | ☐ No |
| 15. Have you ever had an amputation? | ☐ Yes | ☐ No |

Total: _____

## MICHIGAN NEUROPATHY SCREENING INSTRUMENT

**B. Physical Assessment** (To be completed by health professional)

1. Appearance of Feet

| | **Right** | **Left** |
|---|---|---|
| a. Normal | ☐0 Yes ☐1 No | Normal ☐0 Yes ☐1 No |
| b. If no, check all that apply: | | If no, check all that apply: |
| Deformities | ☐ | Deformities ☐ |
| Dry skin, callus | ☐ | Dry skin, callus ☐ |
| Infection | ☐ | Infection ☐ |
| Fissure | ☐ | Fissure ☐ |
| Other | ☐ | Other ☐ |
| specify: _____ | | specify: _____ |

| | **Right** | | **Left** | |
|---|---|---|---|---|
| | Absent | Present | Absent | Present |
| 2. Ulceration | ☐0 | ☐1 | ☐0 | ☐1 |

| | Present | Present/ Reinforcement | Absent | Present | Present/ Reinforcement | Absent |
|---|---|---|---|---|---|---|
| 3. Ankle Reflexes | ☐0 | ☐0.5 | ☐1 | ☐0 | ☐0.5 | ☐1 |
| 4. Vibration perception at great toe | Present ☐0 | Decreased ☐0.5 | Absent ☐1 | Present ☐0 | Decreased ☐0.5 | Absent ☐1 |
| 5. Monofilament | Normal ☐0 | Reduced ☐0.5 | Absent ☐1 | Normal ☐0 | Reduced ☐0.5 | Absent ☐1 |

Signature:_____ Total Score _____ /10 Points

## DIABETIC NEUROPATHY SYMPTOM SCORE

| DNS ITEMS | RATE | POINTS |
|---|---|---|
| Unsteadiness in walking | 0=absent,1=present | |
| Numbness | 0=absent,1=present | |
| Burning,aching pain or tenderness in legs or feet | 0=absent,1=present | |
| Prickling sensations | 0=absent,1=present | |

SCORE:

## PATIENT CONSENT FORM

**STUDY DETAIL : A Study on the prevalence of peripheral neuropathy in patients with chronic kidney disease in GVMCH.**

**STUDY CENTRE :**

**PATIENT'S NAME :**

**PATIENT'S AGE :**

**IDENTIFICATION NUMBER:**

I confirm that I have understood the purpose and procedure of the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.

I understand that the sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However I understand that my identity would not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.

I hereby consent to participate in this study.

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests.

Signature/thumb impression:

Patient's name and address: Place:
Date:

Signature of the investigator:

Name of the investigator: Place:
Date:

: **A STUDY ON THE PREVALENCE OF PERIPHERAL NEUROPATHY IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN GVMCH**

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**2)** **,**

## KEY TO MASTERCHART

1. Height in centimeters.
2. Weight in kilograms.
3. Duration of CKD in months.
4. CKD STAGE 5=V ; 4=IV ; 3= III
5. On HD 1=Yes; 0=No.
6. Duration of HD in months.
7. eGFR value in ml/min/1.73$^2$BSA;calculated by MDRD formula.
8. Serum creatinine in mg/dl.
9. MNSI physical assessment scores out of 10(MAX=10;MIN=0).
10. UPN(Uremic peripheral neuropathy) 1=Present ; 0=Absent.
11. DNSS scores out of 4(MAX=4;MIN=0).
12. Dyslipidemia 1=Present; 0=Absent.
13. T.C=Total cholesterol in mg/dl.
14. TGL=Triglyceride levels in mg/dl.
15. BMI calculated by weight in Kg/Height in metres$^2$.

| S.NO | AGE | GENDER | HEIGHT | WEIGHT | DURATION OF CKD | CKD STAGE | ON HD | DURATION OF HD | EGFR VALUE | Sr. CREATININE | MNSI | UPN | DNSS | Dyslipidemia | T.C | TGL | BMI | Waist cirumference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | 2 | 160 | 60 | 26 | 5 | 1 | 6 | 13.57 | 3.1 | 5 | 1 | 0 | 1 | 201 | 169 | 23.44 | 78 |
| 2 | 52 | 1 | 166 | 59 | 38 | 5 | 1 | 12 | 14.33 | 4.6 | 3 | 1 | 1 | 1 | 226 | 112 | 21.41 | 72 |
| 3 | 36 | 1 | 154 | 67 | 33 | 5 | 1 | 10 | 13.71 | 5.1 | 4 | 1 | 1 | 1 | 212 | 151 | 28.25 | 82 |
| 4 | 45 | 2 | 166 | 88 | 36 | 5 | 1 | 17 | 9.72 | 5.1 | 4 | 1 | 0 | 1 | 202 | 154 | 31.93 | 78 |
| 5 | 41 | 2 | 156 | 57 | 35 | 5 | 1 | 8 | 14.81 | 3.6 | 4 | 1 | 0 | 2 | 192 | 142 | 23.42 | 76 |
| 6 | 28 | 1 | 166 | 88 | 7 | 5 | 1 | 4 | 11.73 | 6.1 | 0 | 0 | 0 | 1 | 278 | 176 | 31.93 | 85 |
| 7 | 36 | 2 | 156 | 57 | 10 | 5 | 1 | 7 | 10.91 | 4.8 | 0 | 0 | 0 | 1 | 216 | 152 | 23.42 | 82 |
| 8 | 48 | 1 | 150 | 54 | 16 | 5 | 1 | 9 | 11.85 | 5.5 | 3 | 1 | 0 | 2 | 172 | 132 | 24 | 78 |
| 9 | 46 | 2 | 176 | 52 | 36 | 5 | 1 | 5 | 9.26 | 5.3 | 5 | 1 | 0 | 2 | 167 | 122 | 16.79 | 73 |
| 10 | 61 | 1 | 156 | 51 | 41 | 5 | 1 | 3 | 14.57 | 4.6 | 7 | 1 | 1 | 2 | 190 | 132 | 20.96 | 74 |
| 11 | 65 | 1 | 179 | 76 | 36 | 5 | 1 | 4 | 9.36 | 6.4 | 4 | 1 | 0 | 1 | 212 | 162 | 23.72 | 80 |
| 12 | 43 | 1 | 164 | 59 | 27 | 5 | 1 | 16 | 14.53 | 4.7 | 3 | 1 | 0 | 2 | 182 | 141 | 21.94 | 75 |
| 13 | 66 | 1 | 162 | 72 | 35 | 5 | 1 | 12 | 10.25 | 5.9 | 5 | 1 | 0 | 1 | 210 | 161 | 27.43 | 81 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 60 | 1 | 158 | 54 | 25 | 5 | 1 | 13 | 7.25 | 8.1 | 5.5 | 1 | 0 | 2 | 192 | 137 | 21.63 | 75 |
| 15 | 40 | 2 | 160 | 59 | 18 | 5 | 1 | 5 | 11.81 | 4.4 | 3.5 | 1 | 1 | 2 | 182 | 148 | 23.05 | 74 |
| 16 | 68 | 1 | 171 | 91 | 26 | 5 | 1 | 7 | 4.86 | 11.2 | 6 | 1 | 2 | 1 | 232 | 168 | 31.12 | 84 |
| 17 | 48 | 1 | 168 | 70 | 33 | 5 | 1 | 9 | 13.87 | 4.8 | 5 | 1 | 3 | 2 | 186 | 132 | 24.8 | 78 |
| 18 | 65 | 2 | 166 | 74 | 41 | 5 | 1 | 12 | 7.94 | 5.7 | 6 | 1 | 1 | 1 | 210 | 162 | 26.85 | 87 |
| 19 | 65 | 1 | 159 | 57 | 27 | 5 | 1 | 10 | 6.48 | 8.9 | 5 | 1 | 1 | 2 | 182 | 132 | 22.55 | 76 |
| 20 | 75 | 2 | 154 | 56 | 35 | 5 | 1 | 7 | 8.82 | 5.2 | 3 | 1 | 1 | 1 | 206 | 154 | 23.61 | 79 |
| 21 | 55 | 1 | 163 | 63 | 29 | 5 | 1 | 2 | 11.29 | 5.6 | 3 | 1 | 2 | 2 | 193 | 142 | 23.71 | 73 |
| 22 | 18 | 1 | 151 | 52 | 12 | 5 | 1 | 4 | 10.77 | 7.1 | 0 | 0 | 0 | 2 | 168 | 132 | 22.81 | 76 |
| 23 | 16 | 1 | 157 | 54 | 8 | 5 | 1 | 5 | 13.66 | 5.9 | 0 | 0 | 0 | 2 | 187 | 122 | 21.95 | 72 |
| 24 | 31 | 1 | 170 | 83 | 26 | 5 | 1 | 20 | 14.8 | 4.9 | 3 | 1 | 1 | 2 | 190 | 143 | 28.72 | 86 |
| 25 | 60 | 1 | 181 | 69 | 23 | 5 | 1 | 10 | 11.1 | 5.6 | 3 | 1 | 1 | 2 | 186 | 122 | 21.1 | 76 |
| 26 | 52 | 2 | 151 | 54 | 37 | 5 | 1 | 3 | 12.87 | 3.9 | 6 | 1 | 0 | 1 | 206 | 166 | 23.68 | 80 |
| 27 | 50 | 2 | 170 | 69 | 34 | 5 | 1 | 7 | 11.59 | 4.3 | 5 | 1 | 0 | 2 | 182 | 132 | 23.88 | 73 |
| 28 | 36 | 1 | 165 | 70 | 26 | 5 | 1 | 6 | 12.31 | 5.6 | 0 | 0 | 0 | 2 | 189 | 148 | 25.71 | 78 |
| 29 | 62 | 2 | 144 | 44 | 45 | 5 | 1 | 7 | 9.11 | 5.1 | 5 | 1 | 1 | 2 | 183 | 137 | 21.22 | 69 |
| 30 | 49 | 1 | 160 | 57 | 27 | 5 | 1 | 9 | 13.81 | 4.8 | 6 | 1 | 0 | 2 | 184 | 146 | 22.27 | 83 |
| 31 | 32 | 1 | 164 | 67 | 16 | 5 | 1 | 12 | 12.61 | 5.6 | 2 | 0 | 0 | 2 | 191 | 147 | 25 | 88 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 | 35 | 1 | 160 | 55 | 26 | 5 | 1 | 23 | 10.42 | 6.5 | 6 | 1 | 0 | 2 | 172 | 137 | 21.48 | 76 |
| 33 | 50 | 1 | 163 | 61 | 28 | 5 | 1 | 12 | 12.83 | 5.1 | 3 | 1 | 0 | 1 | 271 | 167 | 22.96 | 86 |
| 34 | 40 | 1 | 164 | 70 | 25 | 5 | 1 | 8 | 14.39 | 4.8 | 0 | 0 | 0 | 1 | 221 | 162 | 26.03 | 90 |
| 35 | 63 | 1 | 155 | 51 | 46 | 5 | 1 | 8 | 5.09 | 10.9 | 4 | 1 | 1 | 2 | 185 | 139 | 21.23 | 71 |
| 36 | 84 | 1 | 165 | 61 | 22 | 5 | 1 | 10 | 13 | 4.6 | 0 | 0 | 0 | 1 | 261 | 171 | 22.41 | 74 |
| 37 | 45 | 1 | 160 | 60 | 36 | 5 | 1 | 11 | 7.91 | 7.9 | 5 | 1 | 0 | 1 | 268 | 162 | 23.44 | 84 |
| 38 | 50 | 2 | 167 | 55 | 15 | 5 | 1 | 14 | 12.01 | 5.4 | 4 | 1 | 0 | 2 | 161 | 103 | 19.72 | 73 |
| 39 | 57 | 1 | 159 | 56 | 47 | 5 | 1 | 6 | 8.39 | 7.2 | 5 | 1 | 0 | 2 | 187 | 138 | 22.15 | 70 |
| 40 | 46 | 1 | 175 | 61 | 36 | 5 | 1 | 18 | 9.86 | 6.5 | 3 | 1 | 0 | 2 | 173 | 129 | 19.92 | 69 |
| 41 | 29 | 2 | 168 | 67 | 28 | 5 | 1 | 21 | 8.55 | 6.2 | 0 | 0 | 0 | 2 | 191 | 132 | 23.74 | 76 |
| 42 | 52 | 1 | 155 | 69 | 21 | 5 | 1 | 19 | 10.97 | 5.8 | 3 | 1 | 0 | 1 | 254 | 169 | 28.72 | 91 |
| 43 | 22 | 1 | 175 | 64 | 25 | 5 | 1 | 17 | 14.49 | 5.3 | 0 | 0 | 0 | 2 | 175 | 126 | 20.9 | 68 |
| 44 | 38 | 1 | 167 | 72 | 19 | 5 | 1 | 19 | 11.93 | 5.7 | 3 | 1 | 0 | 1 | 161 | 112 | 25.82 | 83 |
| 45 | 35 | 1 | 156 | 54 | 6 | 5 | 1 | 5 | 8.7 | 7.6 | 0 | 0 | 0 | 2 | 183 | 137 | 22.19 | 76 |
| 46 | 68 | 2 | 166 | 56 | 35 | 5 | 1 | 12 | 10.07 | 4.6 | 5 | 1 | 1 | 2 | 179 | 131 | 20.32 | 68 |
| 47 | 36 | 1 | 159 | 53 | 23 | 5 | 1 | 10 | 13.41 | 5.2 | 3 | 1 | 0 | 2 | 176 | 121 | 20.96 | 76 |
| 48 | 35 | 2 | 167 | 64 | 37 | 5 | 1 | 8 | 14.82 | 3.7 | 0 | 0 | 0 | 2 | 198 | 141 | 22.95 | 82 |
| 49 | 53 | 1 | 149 | 51 | 24 | 5 | 1 | 20 | 6.11 | 9.6 | 4 | 1 | 0 | 1 | 239 | 162 | 22.97 | 74 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 50 | 56 | 1 | 162 | 55 | 44 | 5 | 1 | 16 | 5.51 | 10.4 | 5 | 1 | 0 | 1 | 211 | 152 | 20.96 | 72 |
| 51 | 28 | 1 | 160 | 59 | 10 | 5 | 1 | 7 | 14.76 | 5 | 0 | 0 | 0 | 2 | 165 | 121 | 23.05 | 85 |
| 52 | 48 | 1 | 159 | 72 | 23 | 5 | 1 | 12 | 11.37 | 5.7 | 3 | 1 | 0 | 1 | 249 | 163 | 28.48 | 90 |
| 53 | 58 | 1 | 153 | 40 | 35 | 5 | 1 | 14 | 14.38 | 4.5 | 3 | 1 | 0 | 2 | 174 | 135 | 17.09 | 65 |
| 54 | 17 | 1 | 155 | 62 | 15 | 5 | 1 | 10 | 13.24 | 6 | 0 | 0 | 0 | 2 | 171 | 126 | 25.81 | 85 |
| 55 | 48 | 2 | 167 | 62 | 13 | 5 | 1 | 9 | 8.98 | 5.4 | 0 | 0 | 0 | 1 | 205 | 156 | 22.23 | 79 |
| 56 | 47 | 1 | 169 | 60 | 30 | 5 | 1 | 23 | 11.9 | 5.5 | 4 | 1 | 0 | 2 | 179 | 132 | 21.01 | 74 |
| 57 | 32 | 2 | 169 | 59 | 13 | 5 | 1 | 10 | 11.45 | 4.7 | 0 | 0 | 0 | 2 | 162 | 120 | 20.66 | 78 |
| 58 | 60 | 1 | 176 | 65 | 46 | 5 | 1 | 24 | 6.26 | 9.2 | 4 | 1 | 0 | 1 | 208 | 162 | 20.98 | 70 |
| 59 | 60 | 1 | 170 | 85 | 39 | 5 | 1 | 15 | 6.67 | 8.7 | 3 | 1 | 0 | 1 | 331 | 182 | 29.41 | 96 |
| 60 | 21 | 2 | 155 | 77 | 22 | 5 | 1 | 8 | 9.23 | 6.1 | 0 | 0 | 0 | 1 | 301 | 182 | 32.05 | 105 |
| 61 | 35 | 1 | 153 | 45 | 19 | 3 | 0 | 0 | 38.39 | 2.1 | 0 | 0 | 0 | 2 | 168 | 132 | 19.22 | 68 |
| 62 | 32 | 1 | 151 | 68 | 24 | 4 | 0 | 0 | 23.21 | 3.3 | 0 | 0 | 0 | 1 | 298 | 185 | 29.82 | 88 |
| 63 | 72 | 1 | 170 | 60 | 38 | 3 | 0 | 0 | 31.43 | 2.2 | 3 | 1 | 0 | 2 | 185 | 134 | 20.76 | 77 |
| 64 | 40 | 1 | 164 | 62 | 11 | 4 | 0 | 0 | 15.12 | 4.6 | 0 | 0 | 0 | 2 | 192 | 139 | 23.05 | 83 |
| 65 | 57 | 1 | 162 | 56 | 31 | 5 | 0 | 0 | 10.77 | 5.8 | 5 | 1 | 1 | 2 | 165 | 127 | 21.34 | 76 |
| 66 | 53 | 1 | 163 | 54 | 35 | 4 | 0 | 0 | 17.27 | 3.9 | 3 | 1 | 0 | 2 | 156 | 121 | 20.32 | 68 |
| 67 | 60 | 1 | 159 | 72 | 25 | 5 | 0 | 0 | 9.34 | 6.5 | 3 | 1 | 0 | 1 | 365 | 198 | 28.48 | 88 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 68 | 52 | 1 | 163 | 63 | 28 | 5 | 0 | 0 | 11.91 | 5.4 | 3 | 1 | 0 | 1 | 217 | 162 | 23.71 | 85 |
| 69 | 45 | 1 | 159 | 56 | 17 | 5 | 0 | 0 | 8.8 | 7.2 | 2 | 0 | 0 | 2 | 186 | 128 | 22.15 | 82 |
| 70 | 40 | 2 | 167 | 48 | 41 | 3 | 0 | 0 | 31.12 | 1.9 | 0 | 0 | 0 | 2 | 179 | 131 | 17.21 | 65 |
| 71 | 50 | 2 | 170 | 66 | 35 | 5 | 0 | 0 | 12.97 | 3.9 | 0 | 0 | 0 | 2 | 169 | 108 | 22.84 | 79 |
| 72 | 63 | 2 | 163 | 58 | 51 | 4 | 0 | 0 | 18.92 | 2.7 | 4 | 1 | 1 | 1 | 201 | 156 | 21.83 | 75 |
| 73 | 57 | 2 | 162 | 57 | 34 | 5 | 0 | 0 | 14.8 | 3.4 | 3 | 1 | 0 | 2 | 198 | 140 | 21.72 | 76 |
| 74 | 60 | 2 | 165 | 56 | 52 | 5 | 0 | 0 | 11.17 | 4.3 | 4 | 1 | 1 | 2 | 173 | 129 | 20.57 | 67 |
| 75 | 58 | 2 | 162 | 63 | 18 | 4 | 0 | 0 | 25.71 | 2.1 | 0 | 0 | 0 | 1 | 233 | 165 | 24.01 | 87 |
| 76 | 48 | 2 | 161 | 60 | 36 | 5 | 0 | 0 | 6.34 | 7.3 | 3 | 1 | 1 | 2 | 186 | 147 | 23.15 | 85 |
| 77 | 32 | 2 | 158 | 54 | 22 | 4 | 0 | 0 | 19.99 | 2.9 | 0 | 0 | 0 | 2 | 176 | 123 | 21.63 | 73 |
| 78 | 47 | 1 | 162 | 55 | 36 | 4 | 0 | 0 | 15.4 | 4.4 | 4 | 1 | 1 | 2 | 177 | 135 | 20.96 | 69 |
| 79 | 55 | 2 | 171 | 56 | 43 | 4 | 0 | 0 | 16.58 | 3.1 | 3 | 1 | 0 | 2 | 165 | 148 | 19.15 | 74 |
| 80 | 60 | 2 | 164 | 57 | 29 | 4 | 0 | 0 | 17.59 | 2.9 | 4 | 1 | 1 | 2 | 197 | 133 | 21.19 | 80 |
| 81 | 60 | 2 | 166 | 52 | 36 | 5 | 0 | 0 | 6.93 | 6.5 | 3 | 1 | 0 | 2 | 166 | 129 | 18.87 | 68 |
| 82 | 23 | 2 | 153 | 58 | 13 | 5 | 0 | 0 | 14.33 | 4.1 | 0 | 0 | 0 | 2 | 185 | 142 | 24.78 | 86 |
| 83 | 60 | 2 | 156 | 49 | 44 | 3 | 0 | 0 | 32.58 | 1.7 | 0 | 0 | 0 | 2 | 169 | 135 | 20.13 | 72 |
| 84 | 54 | 2 | 171 | 62 | 29 | 4 | 0 | 0 | 17.97 | 2.9 | 0 | 0 | 0 | 2 | 179 | 144 | 21.2 | 76 |
| 85 | 55 | 2 | 173 | 63 | 35 | 4 | 0 | 0 | 15.43 | 3.3 | 3 | 1 | 0 | 2 | 173 | 126 | 21.05 | 79 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 86 | 20 | 2 | 173 | 58 | 42 | 5 | 0 | 0 | 13.24 | 4.5 | 0 | 0 | 0 | 2 | 186 | 121 | 19.38 | 64 |
| 87 | 27 | 2 | 170 | 60 | 27 | 4 | 0 | 0 | 15.62 | 3.7 | 0 | 0 | 0 | 2 | 164 | 119 | 20.76 | 70 |
| 88 | 33 | 2 | 169 | 55 | 15 | 4 | 0 | 0 | 27.32 | 2.2 | 0 | 0 | 0 | 2 | 188 | 140 | 19.26 | 71 |
| 89 | 35 | 2 | 155 | 63 | 23 | 5 | 0 | 0 | 13.94 | 3.9 | 0 | 0 | 0 | 1 | 265 | 165 | 26.22 | 89 |
| 90 | 72 | 1 | 154 | 70 | 46 | 5 | 0 | 0 | 8 | 7.2 | 3 | 1 | 0 | 1 | 324 | 198 | 29.52 | 96 |
| 91 | 54 | 2 | 162 | 63 | 28 | 5 | 0 | 0 | 11.41 | 4.3 | 3 | 1 | 0 | 1 | 236 | 185 | 24.01 | 84 |
| 92 | 50 | 2 | 166 | 58 | 31 | 4 | 0 | 0 | 19.83 | 2.7 | 0 | 0 | 0 | 2 | 185 | 148 | 21.05 | 75 |
| 93 | 43 | 2 | 157 | 64 | 27 | 4 | 0 | 0 | 16.8 | 3.2 | 0 | 0 | 0 | 1 | 225 | 176 | 25.96 | 82 |
| 94 | 60 | 1 | 169 | 57 | 43 | 5 | 0 | 0 | 14.28 | 4.5 | 3 | 1 | 0 | 2 | 177 | 135 | 19.96 | 69 |
| 95 | 29 | 2 | 173 | 60 | 33 | 4 | 0 | 0 | 15.39 | 3.7 | 0 | 0 | 0 | 2 | 189 | 122 | 20.05 | 71 |
| 96 | 28 | 2 | 162 | 47 | 17 | 4 | 0 | 0 | 18.33 | 3.2 | 0 | 0 | 0 | 2 | 178 | 133 | 17.91 | 68 |
| 97 | 72 | 1 | 171 | 65 | 24 | 5 | 0 | 0 | 4.76 | 11.3 | 5 | 1 | 1 | 2 | 168 | 125 | 22.23 | 81 |
| 98 | 53 | 1 | 168 | 72 | 18 | 5 | 0 | 0 | 6.42 | 9.2 | 3 | 1 | 1 | 1 | 208 | 154 | 25.51 | 83 |
| 99 | 63 | 1 | 170 | 62 | 24 | 5 | 0 | 0 | 5.5 | 10.2 | 4 | 1 | 0 | 1 | 289 | 168 | 21.45 | 79 |
| 100 | 78 | 1 | 158 | 54 | 36 | 5 | 0 | 0 | 9.91 | 5.9 | 3 | 1 | 0 | 2 | 187 | 130 | 21.63 | 72 |